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Guideline Development at ECAO (Environmental
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16. ABSTRACT This report summarizes the second of a series of workshop meetings on methods for assessing human health risks from exposure to chemical mixtures sponsored by the Environmental Criteria and Assessment Office (ECAO) of the U.S. Environmental Protection Agency, July 12-13, 1983. The first workshop "Approaches to Risk Assessment for Multiple Chemical Exposures" held in September, 1982 provided a basis for selecting methods to develop into risk assessment guidelines. Five issues were reviewed at this meeting: 1) inter-species conversion of dose and duration of exposure, 2) assessment of risk for less than lifetime exposure to carcinogens and to other toxicants, 3) additivity model for chemical mixtures, 4) methods for determination of acceptable daily intakes from quantal of continuous data, and 5) pharmacokinetic basis of route-to-route conversions. Working groups also produced recommendations for approaches to four additional problems: consideration of high risk subgroups, assessment of multiple routes of exposure, ranking the severity of effects and the use of exposure and monitoring data in health risk assessment. A symposium on this methodology is planned for the fall of 1984. ←		
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Selected Approaches to Risk Assessment for Multiple Chemical Exposures:

Progress Report on Guideline Development at ECAO-Cincinnati

**SELECTED APPROACHES TO RISK ASSESSMENT
FOR MULTIPLE CHEMICAL EXPOSURES**

Progress Report on Guideline Development at ECAO-Cincinnati

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The appendix to this document, consisting of post meeting comments and selected references, will be available only from National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161, as "Selected Approaches to Risk Assessment for Multiple Chemical Exposures: Appendix," EPA-600/9-84-014b.

FOREWORD

Methods must be developed for assessing the potential risks of simultaneous or sequential exposure to multiple chemicals in order to prepare valid assessments of risks posed by environmental contamination. Many real-life exposures have dynamic and chronic patterns that have no counterparts in laboratory studies. This workshop and others in this series are intended to develop such methods, to promote discussion on alternative approaches, and to stimulate research into developing areas in risk assessment.

The need for risk assessment is driven by the presence of or threat of environmental contamination and the absence of sufficient data for the human health effects of these chemicals. The twenty-five peer reviewers listed in this report were selected for their scientific expertise and interest in this pressing problem. The presentations and subsequent scientific interchange among Agency and non-Agency scientists, and the summary statements of the reviewers after the meeting are presented in this document to reflect the dynamic nature of this contemporary problem. The document represents a second progress report on the development of risk assessment methodologies and guidelines which are in progress at the Environmental Criteria and Assessment Office, Cincinnati.

Jerry F. Stara, DVM, DS
Director

ABSTRACT

This report summarizes a workshop that addressed methods and issues for the assessment of human health risks from exposure to multiple chemicals. The meeting was sponsored by the Environmental Criteria and Assessment Office of the U.S. Environmental Protection Agency and was held in Cincinnati, Ohio, on July 12-13, 1983. The methods and issues were selected from those presented at a previous workshop held in September 1982, "Approaches to Risk Assessment for Multiple Chemical Mixtures." Approaches in five areas were discussed with the intention of identifying valid methods of multichemical risk assessment that could be implemented in the near future. Consensus was reached among the participants on approaches to the interspecies conversion of dose and duration of exposure (use one-third power of body weight and lifetime proportionality factors), the assessment of risk for less than lifetime exposure to toxicants (consider dose, duration, and no-effect levels for all available data), and multiple chemical assessment (an additivity model was considered adequate in the interim). The other topics proposed for consensus concerned the assessment of risk for less than lifetime exposure to carcinogens, the determination of acceptable daily intakes based on quantal, continuous, or graded data, and the pharmacokinetic approach to route-to-route conversions.

Brief presentations were made by several participants on approaches using structure-activity relationships, reproductive effects as endpoints in risk assessment, and use and biological justification of mathematical models. Four working groups were also convened to consider approaches proposed in four additional areas: consideration of high risk subgroups, assessment of multiple routes of exposure, the ranking of the severity of the effects, and the use of exposure and monitoring data in health risk assessment. A statement including recommendations was produced by each group as a guide for future discussions. The results of this workshop will provide a basis for developing guidelines for risk assessment from multiple chemical exposures. This effort in guidelines development will culminate in a symposium in the summer of 1984.

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1. INTRODUCTION

MEETING OBJECTIVES AND STRUCTURE (J. Stara)

The U.S. EPA's Environmental Criteria and Assessment Office (ECAO) in Cincinnati sponsored three major workshops that brought together expert scientists to review and discuss guidelines for health risk assessment of chemical mixtures. The purpose of these meetings was to revise and add to the previously published health assessment guidelines (Federal Register, 1980) for assessing the chronic (or lifetime) health risk of single contaminants so that the more complex questions associated with exposures to chemical mixtures could be addressed.

The Agency's interest in the development of risk assessment methodology for multiple chemicals stems from recognition of the nature of actual exposures. The Agency has already regulated public exposure to several mixtures including coke-oven emissions and auto and diesel exhaust. Now, with the implementation of Superfund, the Agency must develop methods for determining the risks posed by what may be thousands of unregulated sites in order to prioritize and direct cleanup efforts. In addition, the Agency must respond to imminent hazards posed by chemical spills, and, toward that goal, ECAO has developed a rapid response assessment system. Toxicity data are stored in a computer and used to make an assessment within 48 hours that can then be provided to state or regional officials. Multichemical assessments also have a role in enforcement, i.e., determining the reduction in risk after a site's cleanup. More broadly, all Agency program offices realize that they are dealing with mixtures, not only single pollutants.

The primary objective of this meeting, therefore, was the injection of scientific stimulus into the development of the multichemical assessment methodologies. To provide structure to this stimulus, this meeting was divided into three sessions.

In Session I, specific selected methodologic approaches were proposed for those subjects that had been discussed at length in previous meetings. Discussion was focused on whether or not the approach was acceptable as stated. If not, an attempt was made to amend the approach to achieve consensus or to clearly identify remaining problems or disagreements. The following topics were presented for consensus: interspecies conversion of dose and duration of exposure; calculation of risk for partial-lifetime exposure to carcinogens or toxicants; calculation of acceptable daily intakes (ADIs) based on quantal, continuous, or graded response data; pharmacokinetic approaches that can be used for conversion among various exposure routes; and methods for multichemical assessment.

In Session II, several new topics were presented that had not been discussed or were only touched upon in previous meetings. One or two speakers were asked to present a brief outline of the issues, followed by a period of discussion. The goal of this session was to elicit comments from reviewers about the direction toward which these issues should be developed. New topics included the use of structure-activity relationships, special methods for reproductive endpoints, and use and biological justification of mathematical models.

Issues introduced at previous meetings, but needing further development, were the subject of four workgroups in Session III. Invited scientists and ECAO staff discussed the strengths and limitations of alternative approaches in order to develop the guidelines in these areas. The objectives of the workgroups were to eventually develop a scientifically defensible consensus reflecting current knowledge and to identify the options that could be best developed into a consensus approach. The following topics were discussed: methods to account for sensitive subgroups, methods to assess effects of multiroute exposures, methods for ranking the severity of various effects, and the use of exposure data in assessing health risk.

2. CONSENSUS TOPICS (SESSION I)

2.1. INTERSPECIES CONVERSION OF DOSE AND DURATION OF EXPOSURE - NONCARCINOGENIC TOXICANTS

2.1.1. Presentation (R. Hertzberg, T. Clarkson). The goal of this session was to choose a method for determining how dose-response information from animal studies could be used to estimate human dose-response relationships for noncarcinogenic toxicants. The primary limitation is that for most chemicals, insufficient data on absorption, metabolism, and elimination are available to accurately extrapolate the dose-duration-effect relationship from studies of animals to humans. Several methods, or options, were proposed for accomplishing these interspecies conversions. To deal with the duration question, a proposed method was to assume that equally toxic effects in humans will result from exposures where duration is the same fraction of the total lifetime as for the exposed animals. This approach is currently used in assessing the risk posed by carcinogens and may be applicable to most noncarcinogenic toxicants. However, it is probably not applicable to certain types of effects, certainly not acute effects and most likely not teratogenic effects that result from exposures during a unique susceptible period.

To deal with the question of equitoxic dose rates, a number of conversion methods were proposed:

1. Expression of dose as a function of body weight, i.e., mg/kg/day
2. Expression of dose as a function of metabolism or some surrogate, i.e., mg/cm² body surface area

3. Use of a mg/kg brain weight per day conversion when extrapolating central nervous system effects
4. Use of Options 1 or 2 when it is known that the substance is detoxified or activated, respectively, in a manner that is similar in the experimental species and humans
5. Use of Options 1 or 2 depending on the best fit of either relationship to the available toxicity data.

None of these options is an obvious choice as the best conversion method. Expression of dose on a straight surface area basis is said to be more "protective" than the body weight-based conversion, because for doses derived in studies with the usual test species, rodents, it results in lower equitoxic doses. Options 4 and 5 are substance-specific: Option 4 requires metabolic data and Option 5 depends on the shape of the dose-response curve derived from toxicity data. However, curve-fitting requires both substantial data and the selection of a justifiable model for the curve-fit.

2.2.2. Discussion. Dr. Clarkson initiated the discussion of duration conversion by stating that the most frequently used approach is to set a proportion between the fraction of the lifetime of the test species for a given effect and the fraction of a human lifetime expected to produce an effect, but that the approach is not applicable to some types of effects, i.e., acute or teratogenic effects. Dr. Hartung pointed out that the question of the validity of the use of proportionality is susceptible to experimental resolution and that consideration of all three axes (dose, duration, and response) should be made. Dr. Nelson indicated that, in general, the dividing line to be considered is between acute effects and delayed effects, and that knowledge of the pharmacokinetics of the substance is needed. Dr. Clarkson responded that pharmacokinetic data are usually

lacking and concluded that there seemed to be general agreement among the participants that EPA should continue to use the lifetime proportionality approach limited by its applicability to only chronic types of effects. He stated that, at this time, this approach is a "best guess" that needs experimental resolution.

In the discussion of dose conversion approaches, Dr. Clarkson stated that body weight, which is proportional to volume, is the preferred conversion and that the rationale for using surface area (because it is an index of metabolic rate) is now believed to be spurious. Dr. Withey pointed out that the important factor to determine is the "effective dose," i.e., the dose at the physiological level that is producing an effect, and that in his published papers Jim Gillette has proposed a conversion approach using effective dose. Dr. Schneiderman pointed out that a conversion could be related to liver weight because the liver is the main site of activation and detoxification; Dr. Clarkson supported the use of a target tissue relationship. Dr. Hattis cited work by Boxenbaum (1982) that demonstrated how many energy-consuming functions display interspecific relations that are a 0.75 power of body weight and therefore the turnover time of the average body constituent is

$$(\text{body weight})^1 / (\text{body weight})^{0.75} = (\text{body weight})^{0.25} \text{ (Hattis).}$$

Dr. Clarkson stated that elimination time is important. He presented data on the elimination rates for methyl mercury in a number of species and showed that the variation between the rates was reduced by a body weight to the one-third adjustment. Several speakers noted that the overall metabolism of a substance (whether it attains a steady state in the blood) would influence any conversion methods based on elimination rates (Hartung,

Nelson, and Nicholson). Dr. Piscator pointed out that when dose is expressed as parts per million of diet, conversions may not be needed because food consumption is proportional to body weight. Difficulties in using dietary concentration alone are that laboratory animals and humans have diets with different composition (low water and fat vs. high water and fat, respectively), and that in some studies the test material influences food consumption (Nisbet).

A proposal for research into the question was made by Dr. Hartung who suggested using a wide range of dose-duration-effect data from different species in an optimization program to determine the best-fitting exponent. Dr. Enslein suggested using structural parameters as covariants, and Dr. Crump proposed analyzing the data with the type of effect as the common denominator rather than the chemical.

In their postmeeting memoranda, several participants provided suggestions for improving interspecies conversions. Dr. Hattis stated that more sophistication could be used in determining a general scaling factor for cases in which the application of Option 4 (pharmacokinetic approach) or Option 5 (goodness-of-fit for toxicity data) were limited by insufficient data. He suggested using the current data base or conducting research to discern patterns in 1) which kinds of chemicals scale with larger vs. smaller body weight exponents, and 2) which kinds of chemicals appear to give rise to anomalous human data (in which direction are the data anomalous and what is the magnitude of the anomaly). In the absence of other information, Dr. Hattis advocated a one-fourth exponent as opposed to one-third.

He also suggested placing the lifespan scaling for duration conversion on a firmer basis by making some comparisons of the "time x dose-rate tradeoff" for a few defined toxic endpoints for several species with different lifespans. Dr. Schneiderman suggested (as did Drs. Hartung and Crump) determining the dose-conversion factor on the basis of a single toxic effect, possibly using for an extrapolation the factor for a "crucial" or "key" toxicity. In their postmeeting memoranda, other participants pointed out additional considerations in interspecies conversions. Dr. O'Flaherty stated that sufficient data were available for a more systematic approach than that used by EPA thus far and raised two questions: 1) Should conversions for short-term (nonsteady-state) exposures be different from conversions for chronic conditions? and 2) how does one perform conversions for compounds that are activated? Dr. Nicholson wrote that the current understanding of interspecies dose conversion for some endpoints, for example cancer, is insufficient for a general policy. He pointed out the strong influence of metabolism on such conversions and cited as an example the 1-4 times higher observed risk in rats than in humans for hemangiosarcoma of the liver caused by exposure to vinyl chloride. Dr. Withey also expressed concern that some species have metabolic deficiencies that alter the metabolism of some classes of compounds such as hexabarbitol and phenols or have different detoxification "priorities"; for example, rodents use glutathione as the primary detoxifying substrate while primates use water and epoxide hydase before glutathione.

2.1.3. Consensus. For interspecies conversion of exposure duration, the consensus was that the lifetime proportionality approach should be used giving consideration to the type of effect being examined, and that the

validity of this approach could be determined by experimentation. For interspecies conversion of dose, the participants decided that the conversion should be based on mg/body weight to the two-thirds power when insufficient data were available to determine a more precise factor; they generally acknowledged that the ideal approach would involve optimization of the exponent in an equation relating dose, species, effect, and body weight (chemical-specific) or dose, species, chemical, and body weight (effect-specific).

2.2. HEALTH RISK ASSESSMENT FOR LESS THAN LIFETIME EXPOSURE - TOXICANTS AND CARCINOGENS

2.2.1. Presentation - Toxicants (M. Dourson). The goal of this subsection was to choose an approach to estimating ADIs for individual substances such as 1) exposure durations less than lifetime when subsequent exposure is assumed to be zero, and 2) exposure duration of any length after known previous exposure. Two options were proposed and illustrated using data on methoxychlor and mirex. In both options, all the available data are plotted on a graph of dose vs. duration. The dose is expressed on a mg/kg basis adjusted by the dose (mg) per surface area conversion for species differences; the duration is the equivalent fraction of human lifespan, i.e., the exposure period of the study in days divided by the assumed or published animal lifespan times 70 years. The results from the study are assigned a code corresponding to severity (Table 2-1), which is based on currently used EPA methodology. The data for methoxychlor are presented in Figure 2-1. The "RP," "GR," "SP," and "LV" notations indicate effects on reproduction, growth, spleen, and liver, respectively. The size of the symbol indicates the relative quality of the study. In Option 1, these data are divided into

TABLE 2-1

Various Effect Levels and Their Definitions

Effect Level	Symbol	Definition
AEL	●	Adverse-Effect Level. That exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.
FEL	▲	Frank-Effect Level. That exposure level that produces unmistakable adverse effects, such as irreversible functional impairment or mortality, at a statistically or biologically significant increase in frequency or severity between an exposed population and its appropriate control.
NOAEL	○	No-Observed-Adverse-Effect Level. That exposure level at which there are no statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control. Effects are produced at this level, but they are not considered to be adverse.
NOEL	◊	No-Observed-Effect Level. That exposure level at which there are no statistically or biologically significant increases in frequency or severity of effects between the exposed population and its appropriate control.
NOFEL	△	No-Observed-Frank-Effect Level. That exposure level at which there are no statistically or biologically significant increases in frequency or severity of frank effects between an exposed population and its appropriate control. Experimenters may or may not have looked for other adverse effects.

four areas corresponding to different durations: acute, short-term, sub-chronic and chronic (Figure 2-2). Highest no-observed-adverse-effect levels (NOAELs) are chosen in each category (indicated by arrows in the figures), and ADIs are estimated using U.S. EPA methods currently in use (Stara et al., 1981). ADIs for subsequent exposures are estimated using the estimated length (duration) of the exposure.

In Option 2, an estimate of the visually best-fitting, highest NOAEL line is made and a corresponding ADI line is drawn. Figure 2-3 presents this option as applied to the methoxychlor data. ADIs for future exposures are determined using the time-weighted average of the previous and subsequent exposure levels. The primary assumptions in developing these plots are that equivalent exposure durations for studies of different species are adequately described by conversion to fractions of expected lifespans and that equivalent doses for experimental animals and humans are derived using a dose equivalence based on surface area.

The advantage of the first option is that it is similar to current U.S. EPA procedures and is consistent with the methods used to estimate health advisories by the Office of Drinking Water. The main disadvantage is that this option does not estimate ADIs using previous exposure information when it is known, a distinct disadvantage when the previous exposure exceeds the ADI for the current duration. Option 2 provides more flexibility in that ADIs can be estimated for any duration once the NOAEL line is established, and thus ADIs for future exposures can be estimated when previous exposures are known.

2.2.2. Discussion - Toxicants. In the discussion, Dr. Schneiderman pointed out that neither option uses all of the available data, rather only the NOAEL points are used in estimating the ADIs. Dr. Hertzberg replied that these options use more data than the current approach and allow one to exercise more judgment, although a statistical method of drawing the NOAEL and ADI lines is preferred.

Several participants provided additional comments in their postmeeting memoranda. Dr. Hattis noted that, although both options are similar, Option 2 is preferable because any division or grouping of data leads to a loss of information. Dr. Silbergeld suggested that for some toxic endpoints, physiologically similar life stages, such as pregnancy or lactation, be used in Option 1 to group the data rather than just the duration of exposure as a fraction of lifespan. Dr. Schneiderman wrote that neither option considers the dose-response relationships observed in the individual experiments, and that a weakness of the approach is that the identification of a NOEL is highly dependent on the sample size, with the smaller sample sizes leading to higher NOELs.

2.2.3. Consensus - Toxicants. In general, the consensus was that the approach is acceptable; neither option was identified as being preferable. The main reservations were that the approach tended to be subjective and that some weighting procedure was needed in drawing the ADI lines to account for the quality of the data.

2.2.4. Presentation - Carcinogens (K. Crump). The goal of the subsession on carcinogens was to identify a method to estimate human lifetime cancer risk from exposures of any duration regardless of age at the start of exposure. The method should also be able to adjust for carcinogens known to act at specific stages of the multistage process now being used by EPA to model carcinogenesis. Three options were suggested:

1. Base all lifetime cancer risk estimates for durations less than lifetime on a ratio of total dose based on exposure to the total dose associated with a given carcinogen potency (q_1^*) and lifetime cancer level (e.g., 10^{-5}).
2. Use the concept of the "Druckrey effect" (i.e., that lower dose rates are more effective than higher dose rates in producing cancer, at a given total dose) in establishing total doses associated with different dose rates and durations for estimating the lifetime cancer risk for durations less than lifetime.
3. Modify the currently used multistage model to allow for estimates of risk from partial lifetime exposure.

Option 1 is currently used by EPA but does not account for the Druckrey effect, the age of initiation of exposure, or the stage at which a carcinogen may act. Option 2 accounts for the Druckrey effect but not the age of initiation or the carcinogen stage. Option 3 would incorporate all three. A method to implement Option 3 was developed under a contract with ECAO (Crump and Howe, 1983).

In his presentation, Dr. Crump pointed out that the basis for his procedure is the Armitage-Doll multistage model of carcinogenesis as refined by Whittemore and Keller (1978) and Day and Brown (1980) to account for noncontinuous exposure and carcinogens that act on different stages. The primary difficulties in the application of his procedure are the selection of the number of stages and the selection of the stage at which the carcinogen

acts. Animal studies have provided few data to identify the number of stages in carcinogenesis, and their applicability to human cancer is in question. Selection of the stage at which a carcinogen acts may be based on the apparent mechanism, i.e., whether it acts as an initiator or as a promoter.

Dr. Crump illustrated his method using data from the NCI bioassay (NCI, 1978) of ethylene dibromide (EDB). The study involved a pattern of high mortality and tumor incidence and an interrupted pattern of dosing (Figure 2-4). Upon fitting the model using different numbers of stages and stages of action, it appeared that the best fit to the data (the fit giving the largest likelihood) had the assumption of six stages with the first stage being dose-related. A comparison of the probability of death from carcinoma of the forestomach (the primary tumor found) as predicted by the model and the Kaplan-Meier estimates found good agreement using all of the data (Figure 2-5) and using the data excluding tumors found at terminal sacrifice (Figure 2-6), because it is questionable whether the tumors found at terminal sacrifice should be used in predicting the probability of cancer death. Table 2-2 illustrates the effect of assuming different stages to be dose-related. The effect on the doses is slight, suggesting that risk estimates from constant dose rates are not extremely sensitive to the stage that is assumed to be dose-related. Table 2-3 shows the effect of a single week of dosing at either week 1, 14, or 30. A dose given at week 14 must be twice as large as the dose given the first week to have the same carcinogenic risk by week 105, and a dose given during week 30 must be about 5 times as large.

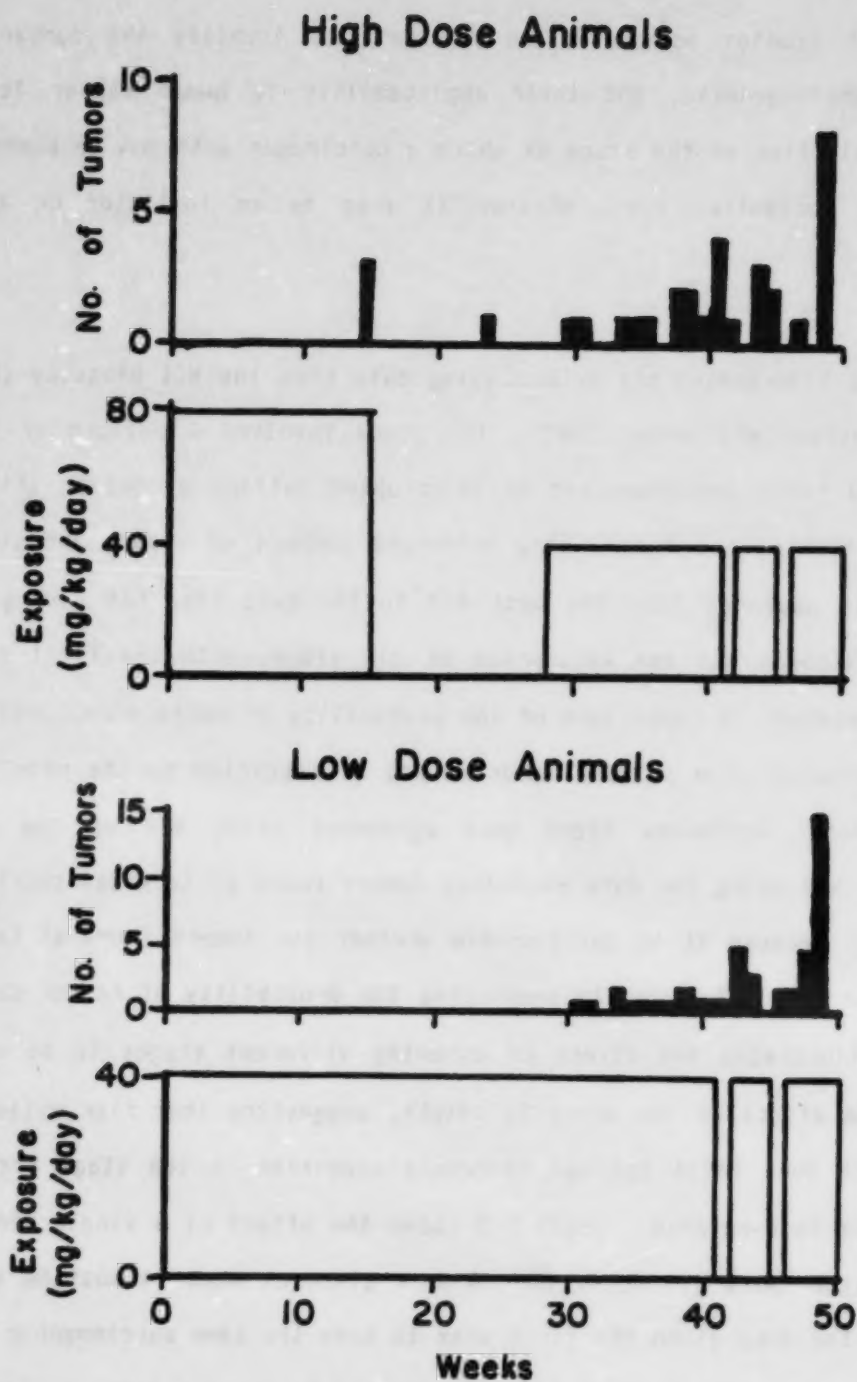


FIGURE 2-4
Male Rats Exposed to EDB by Gavage

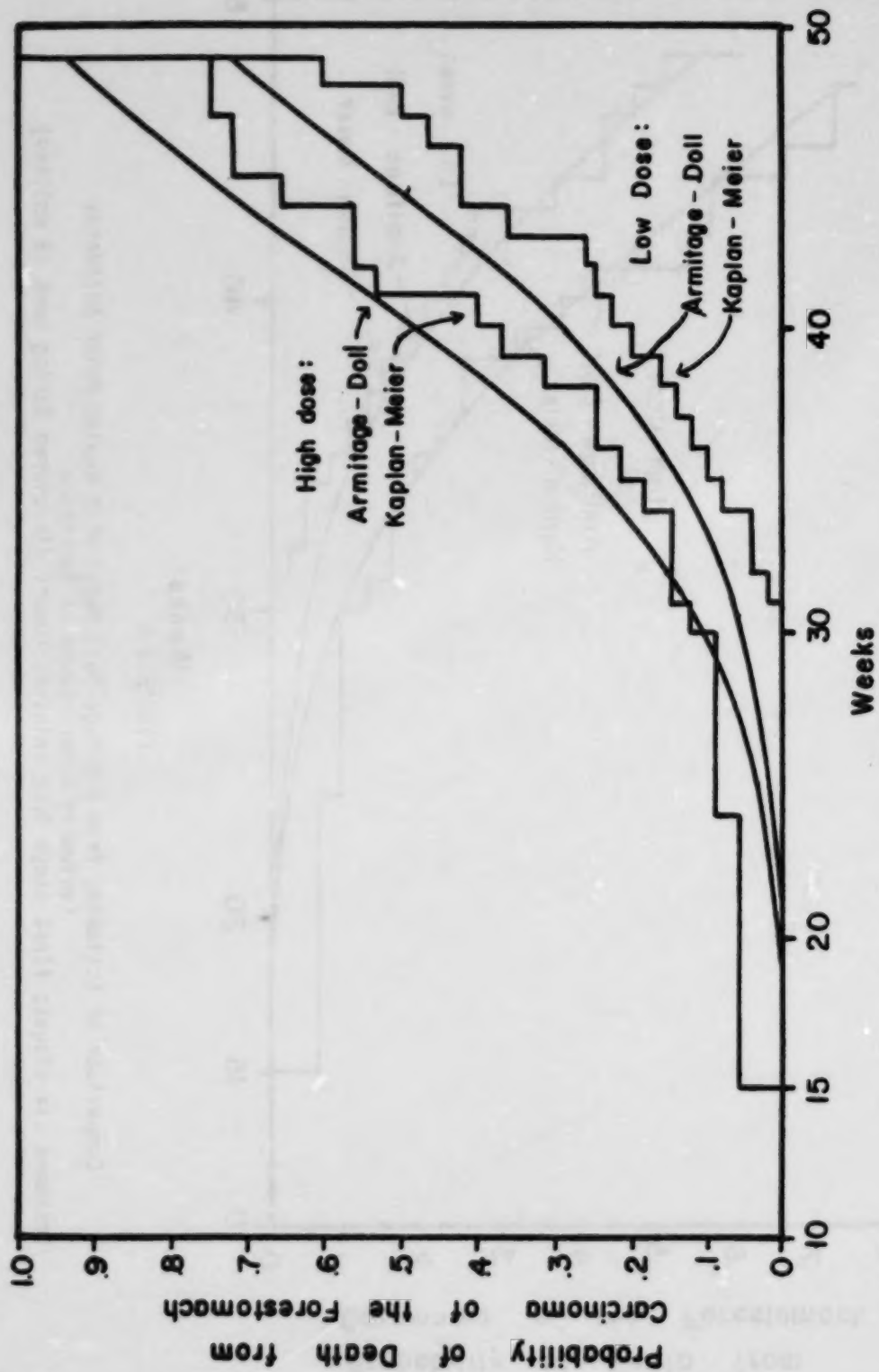


FIGURE 2-5
Comparison of Estimates from Armitage-Doll Model with Kaplan-Meier Estimates
(assumed six stages; first stage dose related)

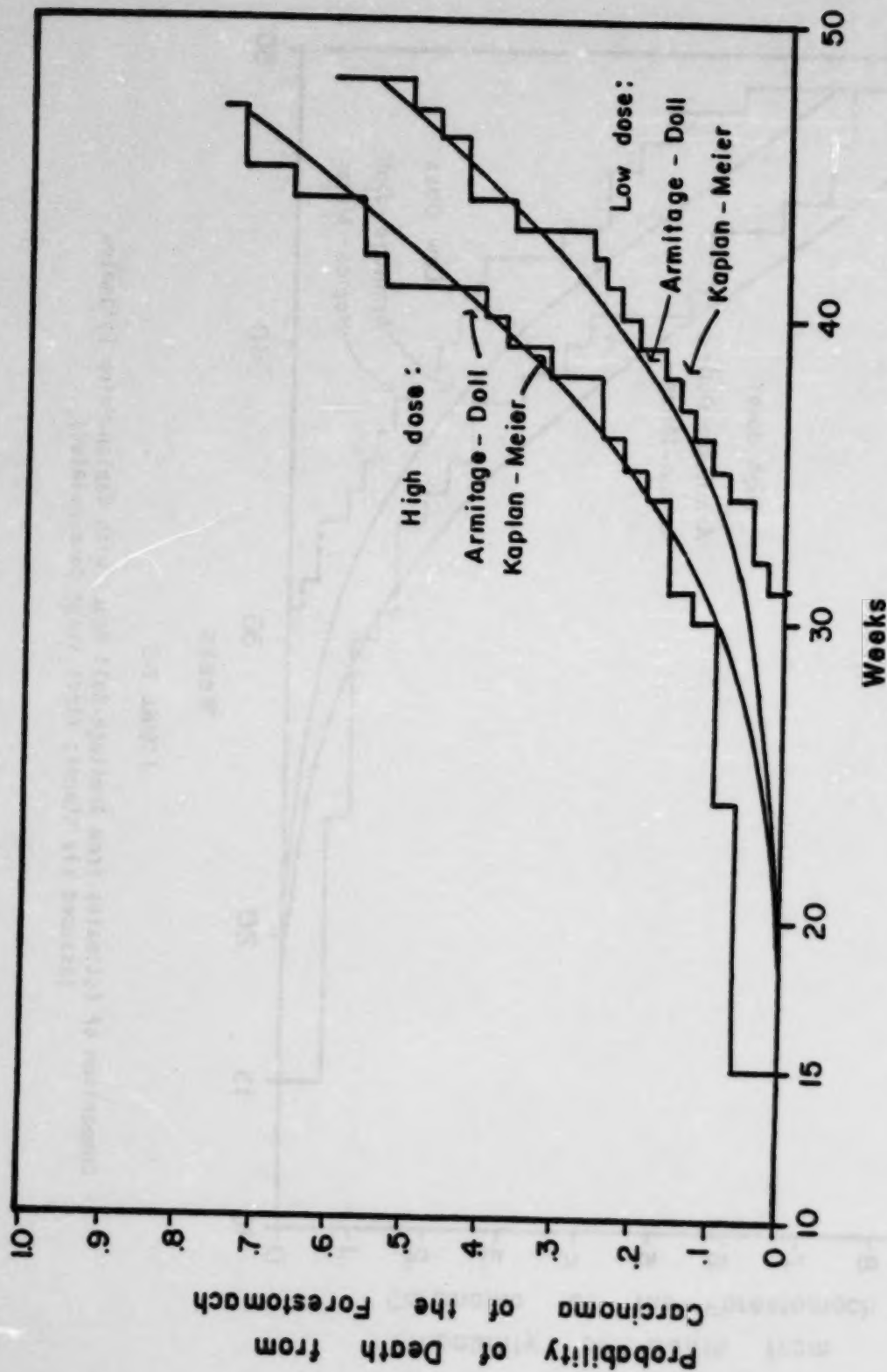


FIGURE 2-6

Comparison of Estimates from Armitage-Doll Model with Kaplan-Meier Estimates
Excluding Tumors Found at Sacrifice
(assumed six stages; first stage dose related; tumors discovered during week 49 omitted)

TABLE 2-2
Constant Dose Rates Corresponding to Given Levels of Extra Risk

Model	Level of Extra Risk*		
	10^{-1}	10^{-2}	10^{-4}
Probability of death from tumor by week 49; 6 stages; stage 1 dose related	3.3 (2.7)	0.31 (0.26)	0.0031 (0.0026)
Probability of death from tumor by week 49; 6 stages; stage 3 dose related	2.5 (2.1)	0.24 (0.20)	0.0024 (0.0020)
Probability of death from tumor by week 49; 6 stages; stage 1 dose related; tumors found during last week of study omitted	4.7 (3.8)	0.45 (0.36)	0.0045 (0.0036)
Probability of tumor by week 49; 6 stages; stage 1 dose related	0.91 (0.70)	0.086 (0.067)	0.00086 (0.00066)
Probability of death from tumor by week 105; 6 stages; stage 1 dose related; tumors found during last week of study disregarded	0.048 (0.037)	0.0046 (0.0035)	4.6×10^{-3} (3.5×10^{-3})

*Maximum likelihood estimates; 95% lower confidence limits in parentheses

TABLE 2-3

Dose of 1-week Duration that Correspond to Given Levels of Extra Risk^a

Beginning of Exposure	Levels of Extra Risk ^b		
	10 ⁻¹	10 ⁻²	10 ⁻⁴
Week 1	0.91 ^b (0.69)	0.087 (0.065)	0.00087 (0.00065)
Week 14	1.8 (1.4)	0.17 (0.13)	0.0017 (0.0013)
Week 30	4.7 (3.7)	0.45 (0.35)	0.0045 (0.0035)

^aExtra probability of death from cancer by 105 weeks; tumors found during last week of study disregarded; 6 stages assumed with stage 1 dose-related.

^bMaximum likelihood estimates; 95% lower confidence limits in parentheses.

2.2.5. Discussion - Carcinogens. Dr. Kuzmack suggested that for the Crump approach to be more practical it should be simplified, possibly by reducing it to a table by making a set of plausible assumptions about likely exposure conditions. Dr. Nisbet pointed out this is feasible because most exposed populations will have both age extremes, and so identification of the carcinogen as early or late stage-acting may not be critical. Drs. Thorslund and Andelman noted that the multistage model does not fit all the sets of data on human cancer, for instance, leukemia. Dr. Crump acknowledged that the multistage model is most applicable to solid tumors, and not leukemias, and that incorporation of pharmacokinetic information would be an improvement in his approach. Dr. Nisbet pointed out that if the assumption is made that most carcinogens act at the first stage, then the risk for promoters with late life exposures will be seriously underestimated. Dr. Nicholson also noted a problem in using animal data to develop models for estimating human risk in that animal studies are not designed to determine the effect of promoters in the same environment of initiators in which humans live. He suggested that animal studies of a suspected promoter should be conducted with concurrent exposure to initiators.

Additional discussion was provided by participants in their postmeeting memoranda. Dr. Hartung believes that the multistage model for cancer induction has been accepted without sufficient scrutiny of its scientific basis. Dr. Hattis stated that he believes the Crump-Howe approach is preferable to the other two options because at least it is based on a hypothesized mechanism of action. Dr. Andelman asked if the concentration (dose) term in the model can be effectively dealt with when it is not a first order variable, i.e., concentration to the 1.2 power, which he felt was not an uncommon situation.

Dr. Schneiderman made both general and specific comments on the Crump-Howe approach in his memorandum. In general, he noted that animal experiments have thus far been capable of identifying only two stages (initiation and promotion) and recommended that both EPA and NTP should design animal models capable of distinguishing more stages and at which stage a carcinogen may be acting. He also stated the Crump-Howe report should be modified to show the effects of a "remaining lifetime" exposure resulting from modifying a dose, rather than showing a fixed number of years of exposure. This would more closely follow the exposure pattern in which the U.S. EPA is interested, where exposures are to be reduced. He also suggested constructing tables from data on carcinogens that appear to act at more than one stage. Dr. Schneiderman made some specific points about the Crump-Howe paper (see Appendix to this report) concerning the expression of cumulative dose in some tables, the 100-fold difference in week 49 stage 1 dose and week 105 in Table 2-2, and the importance of clarifying reasons for nonlinearity.

2.2.6. Consensus - Carcinogens. Dr. Crump's approach was considered to be acceptable in principle with some reservations about its applicability to cancers for which the multistage model of cancer may not apply. Childhood leukemia was given as an example. For these cancers, it was suggested that an ad hoc model be developed based on the available human data.

2.3. ADIs BASED ON QUANTAL, CONTINUOUS, OR GRADED DATA

2.3.1. Presentation (M. Dourson, K. Crump). The goal of this session was to choose a method for estimating ADIs or risk levels for toxicants from

quantal or continuous toxicity data. EPA's current methodology for estimating ADIs is recommended for use with graded toxicity data. Definitions of these three classes of effects data are as follows: graded (or ranked) data are in the form of severity of adverse effects (e.g., fatty infiltration of the liver, single cell liver necrosis, liver necrosis, liver fibrosis) vs. dose without reference to the percentage of animals with the given effect. The data are often considered to be biologically significant by a pathologist, but cannot always be statistically tested. Graded data are frequently reported in the literature. Continuous data are in the form of an increase or decrease in a measured biological parameter (i.e., body weight) vs. dose. The data may be expressed only as an overall average of the experimental animals within a dose group. Quantal effects data are in the form of percentage of animals with a specific endpoint (i.e., death) vs. dose.

Two methods were proposed for using quantal or continuous toxicity data for estimating ADIs. The first option is to fit a mathematical model to dose response data and, using statistical confidence limits, extrapolate downward to doses appropriately safe to humans (i.e., doses corresponding to risks of 10^{-5} or less). The advantage of this approach is that it rewards good experimentation in that experiments with larger numbers of animals (larger number of quantal or continuous data points) tend to produce more narrow confidence limits and consequently higher values for the lower confidence limits of safe doses. It also explicitly takes into account the shape of the dose-response curve because a mathematical model is fit to all of the dose-response data. It provides estimates of risk corresponding to any dose, along with associated confidence limits, and therefore can be

conveniently used in risk-benefit analyses. The method does not, in principle, rule out thresholds because a model that incorporates a threshold can be used for the extrapolation.

The chief disadvantage of an extrapolation approach is related to the selection of the models; different models that fit the observed data about equally well can yield vastly different results when extrapolated to doses corresponding to very small risks. When used in estimating carcinogenic risks, information on the nature of the carcinogenic process has been used in the selection of a model. Most information has indicated that the dose-response curve is apt to be nonthreshold and approximately linear at low doses whenever a chemical initiates cancer through a change in the DNA of a single cell, or whenever background carcinogenesis is present. However, for nongenotoxic events, a linear nonthreshold dose response seems more unlikely. Although a linear model still would define upper bounds to low dose risks, these upper bounds might overestimate the true risk by large amounts in some instances. Thus, the uncertainty as to the true shape of the dose-response curve in the low dose range for nongenotoxic effects and the fact that different models can give vastly different results constitute a disadvantage to the model extrapolation approach for nongenotoxic effects. A second disadvantage to the extrapolation approach is that toxicological experiments are frequently not designed or reported in a manner that facilitates the use of model-fitting methods. Frequently, the doses are selected too far apart to adequately describe the dose-response curve; sometimes the response data necessary for fitting a model are not reported. However, the experimental design and reporting of data in future toxicological experiments could be improved if a model-fitting approach were adopted.

The second option is to fit a mathematical model to dose-response data and, using statistical confidence limits, calculate a lower confidence limit for the dose corresponding to a preset risk of 10^{-1} or 10^{-2} ; then apply a safety or uncertainty factor to this dose that reflects the severity of the toxic effect, the thoroughness of the toxicological study, and possibly the mechanism of action. This approach combines features of the current EPA methodology and Option 1. It shares some of their advantages while avoiding some of their disadvantages. Like Option 1, but unlike EPA methodology, it takes the shape of the dose-response curve explicitly into account. It would reward good experimentation in that larger, better designed experiments should yield higher levels at the lower confidence limits and thereby higher allowable human exposures. Also, it would reduce the problem of the selection of the mathematical model because the estimates from the various models diverge less if extrapolated only down to a risk of 10^{-1} or 10^{-2} . The disadvantages of this approach are that selection of a safety factor could be considered arbitrary and, like Option 1, its experimental design and reporting are often inadequate.

Dr. Crump presented a summary of work he has done on refining the Option 2 approach. He pointed out that the traditional method of determining a NOAEL to which safety factors were applied to estimate an ADI has several limitations: 1) a NOAEL is an experimental dose that results from the study design and does not reflect the entire dose-response relationship; 2) a smaller sample size, i.e., a less reliable experiment, makes it more likely to find a NOAEL; 3) identifying a NOAEL is difficult, especially with continuous data; and 4) some studies are adequately conducted but do not have a NOEL and therefore are not used. In his approach, Dr. Crump proposed

applying one or more models to experimentally derived dose-response data (either quantal or continuous) to identify a "benchmark" dose. The benchmark was defined as a lower statistical confidence limit for the dose corresponding to a specified increase in the level of health effects over the background level. To illustrate this approach, four models (quantal linear regression, quantal polynomial regression, quantal Weibull, and log-normal) were applied to five sets of quantal data (Table 2-4). The results (Table 2-5) indicated good fits (p-value close to 1) for the models with the exception of quantal Weibull and log-normal as applied to the botulinus toxin data, implying that the mechanism of action of the toxin involves a threshold. When maximum likelihood estimates (MLE) and lower confidence limits were calculated for the different models and levels of risk for one data set (Table 2-6), it can be seen that these estimates diverge at the lower levels of risk and yield similar results at the higher levels. Dr. Crump stated that he has applied the approach to continuous data with satisfactory results but did not have time to present them. As a summary, he displayed a comparison of benchmark doses and NOELs for the five data sets (Table 2-7) and pointed out that for four sets the NOEL was between the estimated doses corresponding to 1% and 5% extra risk and that, for the fifth set, his procedure determined a benchmark dose when no NOEL had been identified.

2.3.2. Discussion. Dr. Hartung commented that for any approach to fully utilize all the data and be applicable to all types of responses it must be multidimensional. As an example of data for which the proposed approach may underestimate risk, he selected a continuous response, such as a change in blood pressure, in which a small proportion of the population responded at a low dose of a chemical with severe effects. Other participants also were

TABLE 2-4

Quantal Data Used to Illustrate Quantitative Dose Response Methodology

Ethylenethiourea (ETU) (Khera, 1973)

	Fetal Anomalies in Rats					
Doses (mg/kg):	0	5	10	20	40	80
No. affected/total no.:	0/167	0/132	1/138	14/81	142/178	24/24

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) (Khera and Ruddick, 1973)

	Intestinal Anomalies in Rat Fetuses				
Doses (ug/kg):	0	0.125	0.25	0.5	1.0
No. affected/total no.:	0/24	0/38	1/33	3/31	3/10

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) (Murray, et al. 1979)

	Rats Dead at Birth		
Doses (ug/kg/day):	0	0.001	0.01
No. affected/total no.:	22/318	16/224	17/100

Hexachlorobenzene (HCB) (Khera, 1974)

	14th Rib Anomaly in Rat Fetuses				
Doses (mg/kg):	0	10	20	40	60
No. affected/total no.:	0/80	4/79	8/91	15/87	25/96

Botulinus toxin - Type A (Food Research Institute, Univ. of Wisconsin; see Food Safety Council, 1978)

	Death Due to Botulinus					
Doses (ng):	0.01	0.015	0.020	0.024	0.027	0.030
No. dead/total no.:	0/30	0/30	0/30	0/30	0/30	4/30
Doses (ng):	0.034	0.037	0.040	0.045	0.050	
No. dead/total no.:	11/30	10/30	16/30	26/30	26/30	

TABLE 2-5

Summary of Fits of Models to Quantal Data in Table 2-4

Data	Model*	Chi-square	d.f.	p-value
ETU	QLR	17	3	0.0007
	QPR	0.0	2	1.0
	QW	1.3	2	0.73
	LN	0.46	2	0.93
TCDD	QLR	0.17	2	0.92
	QPR	0.014	1	0.91
	QW	0.32	3	0.85
	LN	0.23	3	0.89
TCDD	QLR	0		
	QPR			
	QW	0		
	LN	0		
HCB	QLR	0.11	2	0.95
	QPR	0.09	1	0.76
	QW	0.11	2	0.95
	LN	0.31	2	0.86
Botulinus toxin	QLR	7.0	8	0.54
	QPR	4.4	7	0.73
	QW	162	8	0.00001
	LN	159	8	0.00001

*QLR = Quantal linear regression (with a threshold)

QPR = Quantal polynomial regression (with a threshold)

QW = Quantal Weibull (without a threshold)

LN = Log-normal (without a threshold)

TABLE 2-6
Doses Corresponding to Given Levels of Extra Risk for Quantal ETU Data

Model	Extra Risk	Doses (mg/kg)		
		MLE ^a	95% Lower	99% Lower
QLR	0.1	12.2	11.8	11.6
QPR		16.4	13.9	13.2
QW		17.9	15.7	14.7
LN		17.1	15.3	14.6
QLR	0.05	11.0	10.6	10.4
QPR		13.2	11.6	11.0
QW		14.5	12.2	11.3
LN		14.8	13.0	12.2
QLR	0.01	10.1	9.7	9.5
QPR		10.2	7.2	6.0
QW		8.9	7.0	6.2
LN		11.2	9.5	8.8
QLR	1 x 10 ⁻⁶	9.9	9.5	9.2
QPR		9.4	4.0-1	1.5-3 ^b
QW		5.9-1	2.9-1	2.1-1
LN		4.2	3.1	4.7

^aMaximum likelihood estimates

^b1.5 x 10⁻³

TABLE 2-7

Comparison of Benchmark Doses with NOELs for Quantal Data

Data Set	Units	NOEL	Benchmark Doses* Corresponding to Extra Risk of		
			10%	5%	1%
ETU	mg/kg	5	13.9	11.6	7.2
TCDD	ug/kg	0.125	0.32	0.22	0.049
TCDD	ug/kg/day	1.0-3	5.3-3	2.6-3	5.1-4
HCB	mg/kg	ND	17.4	8.5	1.7
Botulinus toxin	ng	0.027	0.029	0.027	0.025

*95% lower limits derived from QPR model

ND = Not determined

concerned that the approach may imply the existence of a threshold below which no effect would be expected, especially considering the wide variation in individual thresholds in the human population (Kuzmack, Nelson, Hattis). Dr. Crump responded that the models he used incorporating thresholds were found to fit some data sets the best, and that his method was not designed to determine a threshold but a dose that corresponds to a low level of risk. Dr. Silbergeld and others (Nisbet, O'Flaherty) felt that more discussion was needed on the application of the model to continuous data and on the conversion of one type of data to another, i.e., continuous to quantal. Dr. Stara suggested that Dr. Crump's complete paper be distributed by ECAO to the participants to provide the details of the applicability of the approach to quantal and continuous data.

Some of the participants provided written comments on the proposed approach in their postmeeting memoranda. Dr. Schneiderman noted that the benchmark approach (Option 2) has the same difficulties as those of modeling carcinogenesis data, for example, how to choose a model that accurately reflects the data including the presence or absence of an observed threshold. Dr. Silbergeld also cited difficulties with the proposed benchmark approach in that the wide variation in the severity of effects would complicate the selection of the safety factors that are applied to the benchmark values. Dr. Nisbet wrote that for "truly QCG [quantal, continuous, graded] data" derivation of an ADI is inappropriate because such data can often be fitted to a nonthreshold model.

Dr. Hattis pointed out in his memorandum that a major problem is that the steepness of the dose-response curve depends on the genetic diversity of

the exposed population and therefore animal data are likely to produce a steeper curve than that expected for humans and lead to an underestimation of risk. He also proposed modifying Option 2 by the use of different safety factors for different effects depending on the likely distribution of susceptibility in the exposed human population and on policy judgments about the severity and socially desirable protective posture for different effects. Dr. O'Flaherty also suggested a modification to make the approach relatively model independent. When working with quantal data, she proposed the calculation of a confidence limit on the dose corresponding to a specified low risk (i.e., 10^{-2}) and then the application of appropriate uncertainty factors. She also pointed out that in the application of the approach to quantal data, which vary from 0 to 1.0, selection of the uncertainty factors should take this variability into account.

2.3.3. Consensus. The consensus of the participants was that Dr. Crump's benchmark approach was conceptually acceptable but that no decision could be made on how to go from a benchmark dose to an ADI, which would be certain to provide adequate protection for all members of a human population. Additional consideration of the applicability of the approach to continuous data was also indicated.

2.4. PHARMACOKINETIC APPROACH FOR ROUTE-TO-ROUTE CONVERSION

2.4.1. Presentation (W. Pepelko, J. Withey). Dr. Pepelko proposed that consensus be sought in three areas. First, that the primary routes of concern for human exposure are inhalation and oral and that data from animal studies using different routes be used when such factors as absorption

efficiency, dose frequency, and hepatic metabolism are known and taken into consideration. Second, that extrapolation, especially from oral to inhalation and vice versa, is feasible under the following conditions: 1) if the portal of entry is not the target organ, 2) if the toxicant chemical is not totally inactivated before reaching the target organ, and 3) if elimination rates are sufficiently slow that blood levels do not fluctuate greatly during periodic dosing. Third, that the extrapolation procedure account for any factor that affects the concentration of the toxicant at the target organ and is different for different routes, including absorption efficiency and the degree of activation or deactivation before reaching the target organ. Dr. Pepelko stated that the primary considerations are the conditions under which the results from one route of exposure can be converted to another and how that conversion is to be accomplished.

In his presentation, Dr. Withey reviewed graphical comparisons of the dose levels in blood achieved by inhalation exposure, 4 oral doses, and 20 oral doses in a one-compartment pharmacokinetic model in which total uptakes for each exposure were equal. In the first case, where a short elimination time is assumed (Figure 2-7), it was evident that the four oral doses lead to much higher blood levels, which could greatly affect the type or severity of the effects observed. In the two other cases, in which intermediate elimination rates (Figure 2-8) and very long elimination rates (Figure 2-9) were assumed, the blood levels for the three administrations were seen to converge. From these data, Dr. Withey concluded that increasing the frequency of the dose gives a closer approximation of oral uptake to steady-state inhalation systemic levels, and fast elimination rates (short $t_{1/2}$) give larger fluctuations about the steady-state level.

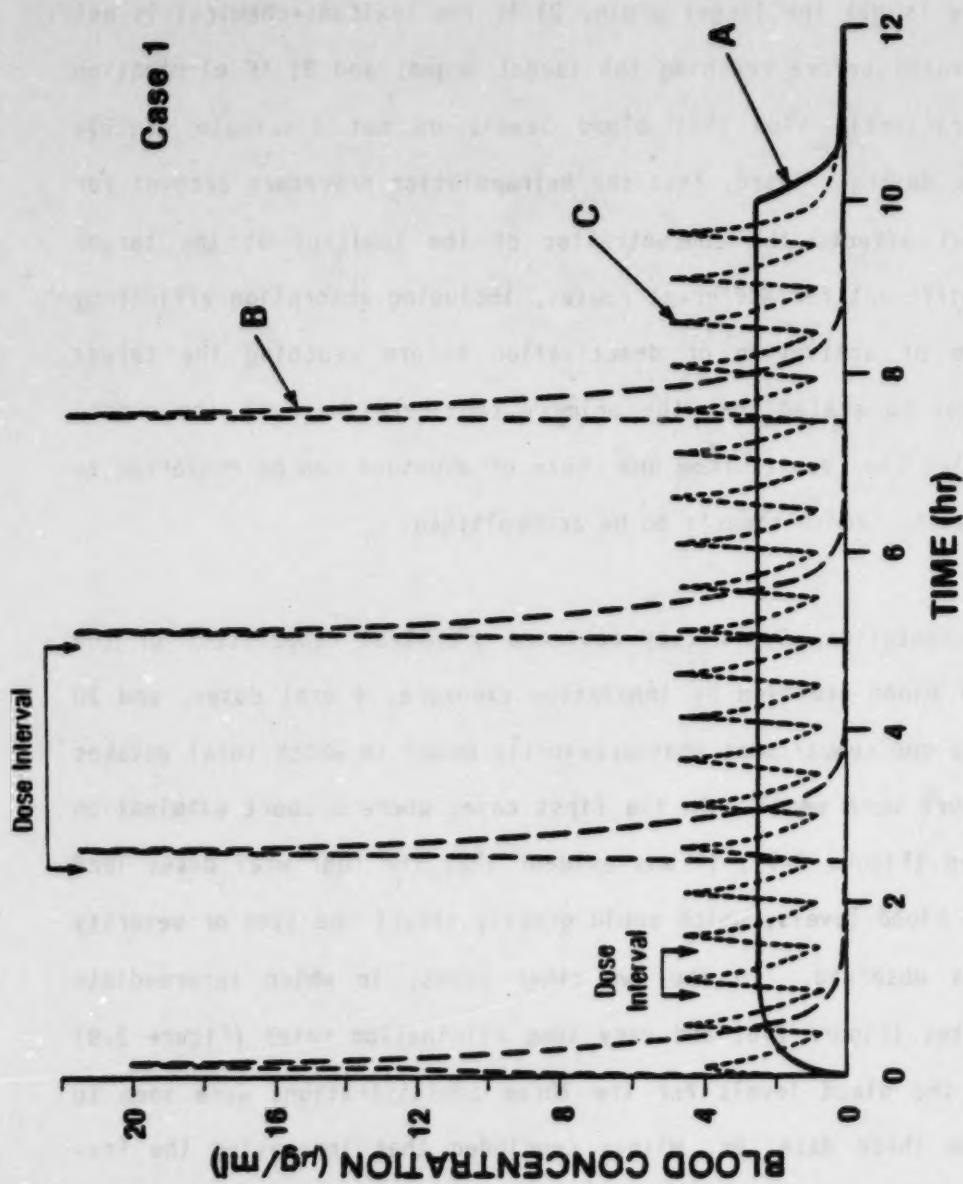


FIGURE 2-7
Hypothetical Blood Concentrations for Three Exposure Conditions:
Inhalation, 4 Oral Doses, and 20 Oral Doses

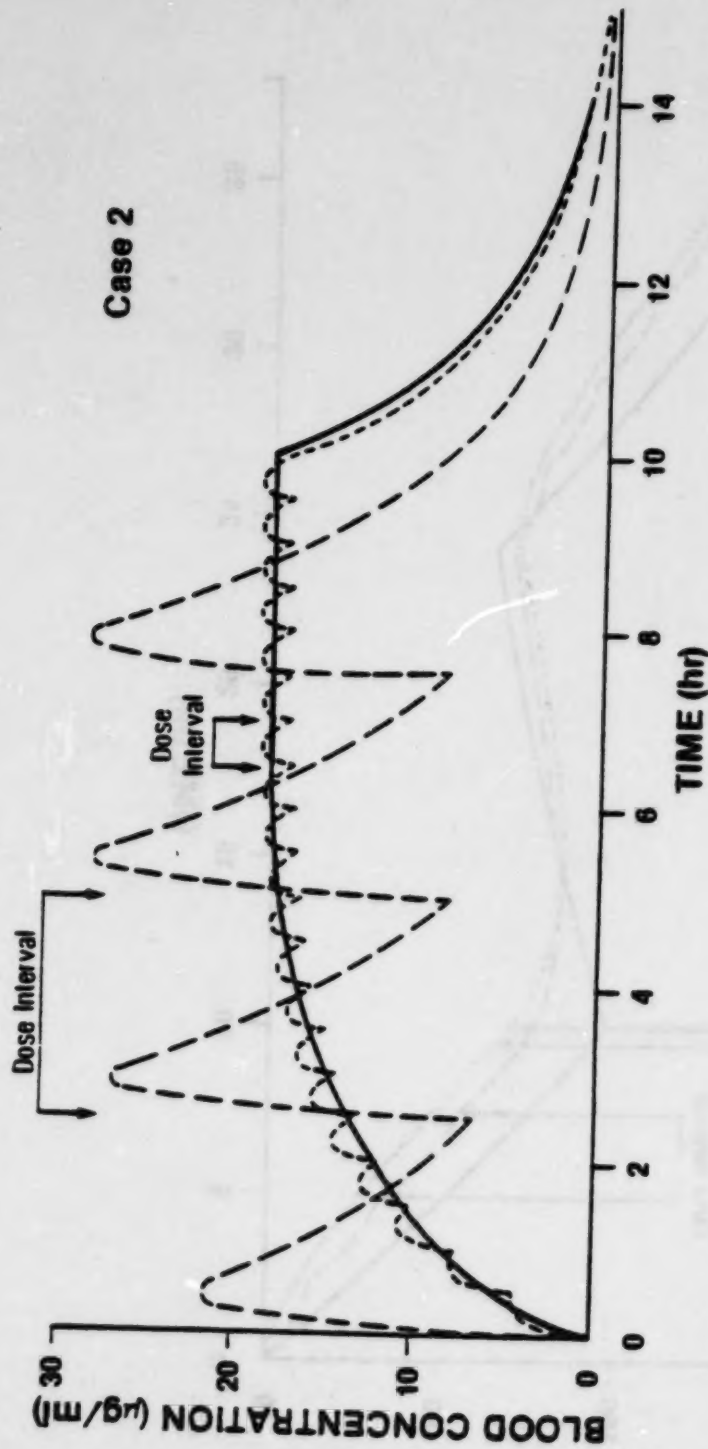


FIGURE 2-8

Hypothetical Blood Concentrations for Intermediate Elimination Rates

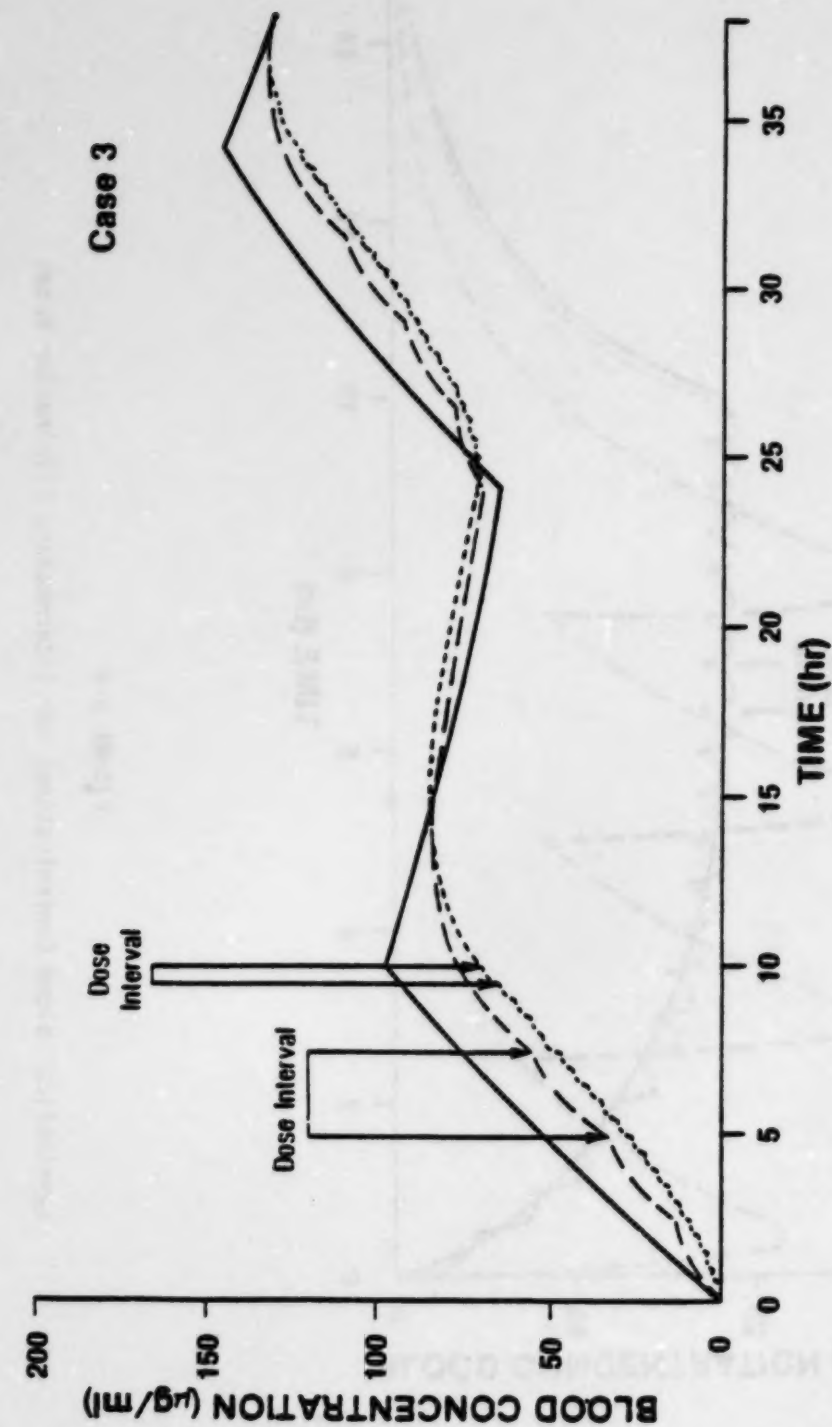


FIGURE 2-9
Hypothetical Blood Concentrations for Long Elimination Rates

In the text of his presentation, Dr. Withey also stated: "It is worthwhile to point out that, where a compound is absorbed relatively rapidly and eliminated slowly, the dose interval and regimen do not influence the systemic concentration or their temporal relationship, as shown in case 3. In such circumstances it is the amount rather than the kinetics of systemic uptake and elimination that would be expected to influence the systemic toxicity. In these cases, provided that the inhalation TLV is soundly based (i.e., there is little involvement of first pass effects, organohepatic or site of uptake effects are not the index of toxicity, etc.) and absorption coefficients are known, there would appear to be no reason why the oral equivalent could not be calculated using the Stokinger-Woodward approach."

Dr. Withey pointed out that at the previous meeting, Dr. O'Flaherty had discussed an important consideration in route-to-route conversions: the special case of the deposition of aerosols and particulates in the lung. Deposition varies with particle size but, once deposition occurs, uptake (at least of aerosols) is remarkably similar, regardless of particle size. The amounts cleared from the lung are not proportional to lung deposition. These considerations are important in the assessment of certain kinds of pulmonary uptake and in addressing special mechanisms associated with route.

Dr. Withey also mentioned the importance of the first-pass effect because it is very much dependent on route. "Substances injected intravenously or absorbed via the lung are carried, and distributed, more or less equally to the vessel-rich organs of the body. Substances administered orally pass from the gastrointestinal tract via the portal system and into the liver. Thus, for substances that are subject to extensive hepatic

metabolism, the effective dose reaching the systemic circulation is considerably reduced (in the case of lidocaine, for example, 100% of an oral dose is metabolized on first pass through the liver)." Similarly, compounds that are activated by the liver may have exposure route-specific patterns of toxicity because of the first-pass effect.

Dr. Withey reviewed the need for route-to-route conversion methods. "First, the absence or lack of adequate studies for the route of interest in humans may necessitate the use of pharmacokinetic principles for an estimation of toxic insult. This will include experiments that have been poorly designed or executed, in terms of dose, duration, numbers, etc., or practical considerations like low aqueous solubility, which preclude toxicity studies in drinking water, the use of an inappropriate dosing vehicle, for example, vegetable or mineral oil as opposed to water, and animal data where the pharmacokinetic rates and mechanisms are species-, sex-, or strain-dependent and extrapolation is precluded." Second, potentially useful data may be available from human or animal studies in which the route has been intravenous, subcutaneous, intramuscular, intraperitoneal, etc. He pointed out that the data from such studies may be acceptable in every other sense and, if there is no reason to suppose that metabolic processes or other factors are affecting the blood levels, the data should be extrapolated to a more conventional route. However, he noted that enormous amounts of data may be needed in order to derive a defensible estimate.

Dr. Withey also cited the following as information requirements for undertaking the application of any route extrapolation methodology:

1. Nature of the pharmacokinetic model.
(one-, two-, or multicompartement, Michaelis-Menten)
2. Nature of exposure.
(Dose and dose interval/duration)
3. Absorption efficiency.
4. Hybrid rate coefficients for absorption and elimination and their variation with dose.
5. First-pass effect (magnitude).
6. Are metabolites the active toxicant?
7. Are metabolic pathways the same?
8. Are metabolic rates the same?
9. Is systemic concentration proportional to toxic effect?
10. Potentiation/antagonism on repeated dosing.

Dr. Withey pointed out that in his three original examples where he made fairly realistic assumptions (100% uptake, uptake the same for all routes, absorption rate equal to 10 times the elimination rate), the acceptability of route extrapolation would be poor, questionable, and excellent, respectively (Table 2-8). Much would depend, however, on the specifics of particular exposure patterns, physicochemical properties, etc. He stated that "route extrapolation may thus be reduced from a generalized to a case-by-case consideration, particularly where mechanisms, species differences, and other parameters, like those considered above, are involved. It would, at this stage, be unfair and inappropriate to put precisely defined limits on the application of pharmacokinetic principles to the question of route extrapolation."

TABLE 2-8
Magnitude of Rate Coefficients ($t_{1/2}$)

	Absorption ($t_{1/2}$) minutes	Elimination ($t_{1/2}$) minutes	Extrapolation Ability
Case 1	0.9	9.0	Poor
Case 2	6.9	69.0	Questionable
Case 3	144.0	1440.0	Excellent

Dr. Withey displayed the equation he uses to calculate blood levels in his one-compartment model and pointed out that the critical factor is knowing the absorption efficiency, which in turn requires a great deal of data to determine. He said, "It has been suggested that, where the site of uptake, or portal of entry, is the primary target tissue (as it is in the case of pulmonary damage arising from the inhalation of manganese or chromium), the application of either pharmacokinetics or route extrapolation is precluded. In the case where the target organ is the same for both inhalation and systemic [gastrointestinal] uptake, as it is in the case of paraquat, a special consideration of the relative insult arising from the administration of equivalent doses would be a rewarding test of the strength and the value of pharmacokinetics as a predictive tool." Finally, Dr. Withey pointed out that the choice of the pharmacokinetic model is also important; the addition of compartments to the model or an increase in elimination rate can greatly alter the blood profiles. Another complicating factor is that the pharmacokinetics may be changed by the test substance; for example, the steady state blood levels increase or decrease considerably in the simple model when the elimination rate is increased or decreased, respectively, during the administration.

2.4.2. Discussion. Dr. Stara pointed out that the assessment of exposure to particulates is complicated by the observation that inhaled materials are often cleared from the lungs and swallowed, resulting in gastrointestinal absorption, but that the Stokinger-Woodward approach should work for inhaled solvents. Dr. Withey noted that this approach may not apply to highly volatile solvents and that the important factor is the absorption efficiency.

Dr. Piscator stated that the Stokinger-Woodward approach should be used with caution in determining ADIs because it is based on threshold limit values (TLVs) and not directly on the data from which the TLVs are derived. Dr. Stara agreed that some values have limited documentation. Dr. Hartung made the point that although it is important to know if the substance is having an effect at the portal of entry, these data are usually not collected. Dr. O'Flaherty noted that Dr. Withey's analysis of the variation in blood levels from different routes also indicated that different levels result from intermittent dosing of different frequency within the same route.

2.4.3. Consensus. No consensus was sought at this point. Additional discussion and an attempt to achieve consensus occurred in the workshop on Multiple Route Exposure, which is summarized in Section 4.2.

2.5. MULTIPLE CHEMICAL ASSESSMENT

2.5.1. Presentation (R. Hertzberg, P. Durkin). The goal of this session was to choose an approach to evaluate health risks from exposure to a mixture of chemicals in the absence of information on their possible interaction. Two options were presented for discussion. In the first, the risk assessment is based on a single chemical, the marker chemical, which is believed to present the greatest hazard as determined by its toxicity and by the ratio of the actual exposure to the current regulatory criterion value. When no criterion has been established, the lifetime threshold concentration (the level considered acceptable for lifetime exposure) or the 10^{-5} risk-specific concentration is used. In this option, the assessment is a rough estimate of risk and is unlikely to be overinterpreted; however, only a small part of the available data is actually used in the assessment.

The second option and its background was presented by Dr. Durkin, who stated at the outset that this approach is a "default position," i.e., one that he proposes in the absence of data on how chemicals interact at low doses. He pointed out that there are two general approaches to assessing the effects of mixtures of chemicals: dose addition and response addition. In dose addition, the assumption is, if the dose-response relationship is known for the substances, then one can be treated as a dilution or concentration of the other depending on its relative potency, which is a ratio of equitoxic doses. Figure 2-10 shows how the doses of two chemicals (y_1 and y_2) are combined into a single expression utilizing potency. In response addition, the expected response is assumed to depend on the response caused by toxicants 1 and 2 alone and on the degree of correlation of the tolerances to the two chemicals within the exposed population. Hence, if the animals that are sensitive to 1 are also sensitive to 2 [i.e., the correlation r is 1 and the proportion of the animals responding to 1 alone is greater than the response to 2 ($P_1 > P_2$)], then the response to the combined exposure is equal to the response of 1 ($P_3 = P_1$; Equation 1, Figure 2-11). If the correlation is zero, equation 3 is used, and if there is a perfect negative correlation of equitoxic doses of tolerances, the proportion responding is equal to the sum of the individual responses (Equation 4, Figure 2-11). These relationships can be displayed graphically on an isobole diagram (Figure 2-12).

As an example of how the different assumptions of dose or response additivity can produce different expected responses, Dr. Durkin gave the example in Figure 2-13, in which the proportion of the population responding to a mixture of equitoxic doses of toxicants 1 and 2 ranged from 20-53%. He also

$$y_1 = a_1 + B \log z_1$$

$$y_2 = a_2 + B \log z_2$$

$$Y = a_1 + B \log (z_1 + pz_2)$$

p = POTENCY : RATIO OF EQUITOXIC DOSES

$$\log p = (a_2 - a_1) \div B$$

FIGURE 2-10

Dose Addition

-
- 1) $P_3 = P_1$ $\text{IF } r = 1 \text{ AND } P_1 > P_2$
- 2) $P_3 = P_2$ $\text{IF } r = 1 \text{ AND } P_2 > P_1$
- 3) $P_3 = P_1 + P_2(1 - P_1)$ $\text{IF } r = 0$
- 4) $P_3 = P_1 + P_2 \leq 1$ $\text{IF } r = -1$

FIGURE 2-11
Response Addition

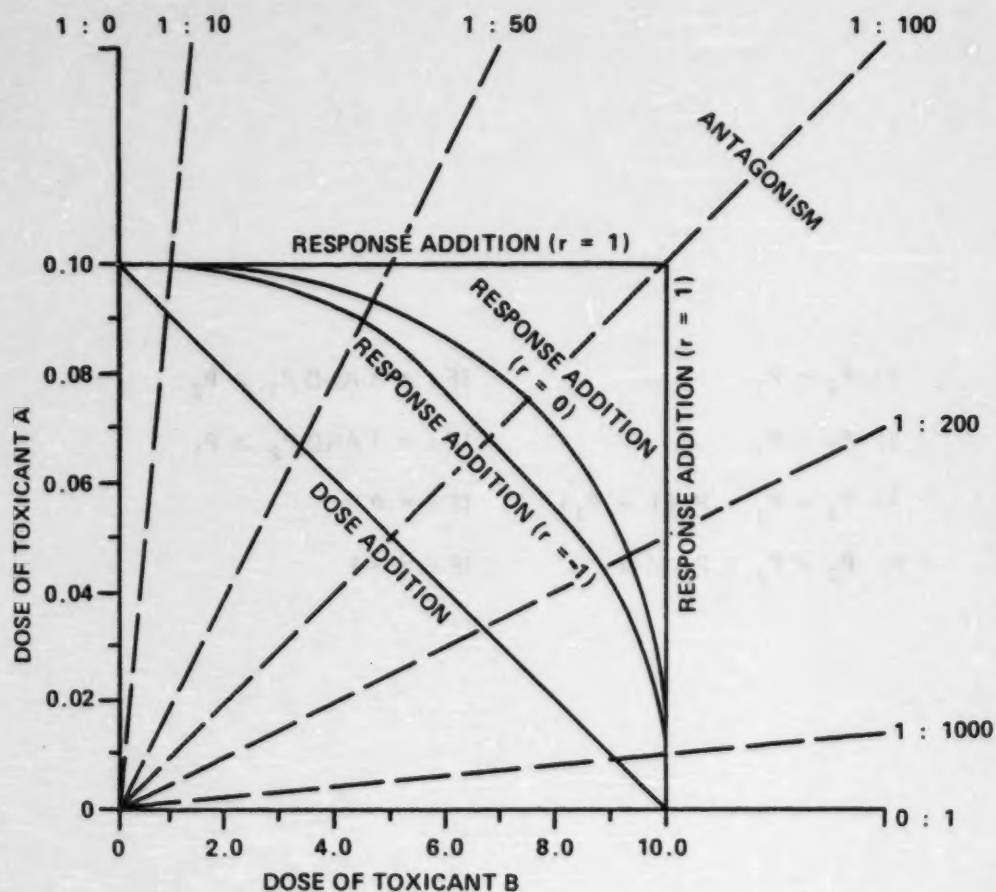


FIGURE 2-12
Isobole Diagram for Quantal Response Data
Source: Muska and Weber, 1977

$$y_1 = 0.3 + 3 \log 19.3$$

$$y_2 = 1.2 + 3 \log 9.7$$

EXPECTED RESPONSE

DOSE ADDITION	53%
RESPONSE ADDITION	20% (r = 1)
	36% (r = 0)
	40% (r = -1)

FIGURE 2-13

Example of Dose and Response Addition

pointed out that as the expected responses get smaller, the differences between the predictions also become less with the exception that, as long as equitoxic doses are used, a completely negative correlation of responses will always produce a combined response two times the combined response of a completely positive correlation.

Dr. Durkin also reviewed models of interactions he had presented at an earlier meeting (Figure 2-14). Equation 1 is a rearrangement of the model for dose addition and does not show any interaction. In Equation 2, the interaction of the two chemicals is accounted for by the K coefficient which is a constant, p is the relative potency, and π_1 and π_2 are the proportions of toxicants 1 and 2 in the mixture. Equation 3 was developed by Dr. Durkin to model interactions in which the interaction may change with dose and therefore has two interaction coefficients. Dr. Durkin also pointed out that the use of these models is limited by the lack of data to determine the individual toxicant's dose-response relations and the interaction of the toxicants. He stated that his survey of the literature on chronic effects found very little data on interactions and that this was clearly not the approach to use.

The approach recommended by Dr. Durkin (Option 2) consists of separate procedures for noncarcinogens and carcinogens. For noncarcinogens, a "hazard index" (HI) is estimated for each chemical by the sum of the exposure levels (E) for each route (O = oral, I = inhalation, D = dermal) weighted by the inverse of the respective lifetime threshold concentrations (Th):

$$HI = E_O/Th_O + E_I/Th_I + E_D/Th_D$$

$$1) y = a_1 + B \log (\pi_1 + p\pi_2) + B \log z$$

$$2) y = a_1 + B \log [\pi_1 + p\pi_2 + K (p\pi_1 \pi_2)^{0.5}] + B \log z$$

$$3) y = a_1 + B \log [\pi_1 + p\pi_2 + K_1 \pi_1 (p\pi_1 \pi_2)^{0.5} + K_2 \pi_2 (p\pi_1 \pi_2)^{0.5}] + B \log X$$

FIGURE 2-14

Models for Interaction

The total hazard index (HI_T) is estimated by the sum of the individual chemical indices and, when greater than one, is considered to be a cause for concern:

$$HI_T = HI_1 + \dots + HI_n \text{ for } n \text{ chemicals}$$

For carcinogens, the procedure is a generalized additive response model assuming a zero correlation of tolerances, i.e., that the risks are independent. For each chemical, the proportion of responders in a population is determined by adding the risks from each route of exposure. Then, the total risk for a mixture of n chemicals is as follows:

$$R_T = 1 - \prod_{i=1}^n (1 - R_i)$$

where R_i is the risk by all routes for i . The merits of this option for both carcinogens and noncarcinogens are that all routes and chemicals contribute to the risk estimate and hence more data are used than in Option 1. The assumptions of independence of action and additivity of effect, however, probably oversimplify the actual situation. In addition, Dr. Durkin noted that it is not certain that the types of interaction mechanisms observed at high doses are applicable to low doses, and thus, much more information is needed to verify this approach.

2.5.2. Discussion. The primary points of discussion were 1) whether all effects could be considered equivalent, since values of HI based on different effects are summed to derive HI_T (Silbergeld, Lappenbusch), and

2) whether subthreshold effects of different chemicals are additive (Hartung, Piscator). Dr. Piscator made the point that if sufficient data were available to predict interactions, then enough data would be available to do a chemical-by-chemical assessment and a possibly misleading total is not needed. Other participants noted that, in general terms, it is likely that the total effect of a multichemical exposure will be the sum of individual effects (Schneiderman) and that individuals in a population will display different susceptibilities to chemicals (Nelson). Dr. Andelman expressed concern that for the noncarcinogens in the additive model, a total of 1 or more was cause for concern while lower values were not and suggested that the approach be used as a relative ranking of risks. Dr. Hartung stated that the approach should be termed "the best speculation" at this time.

In their postmeeting memoranda, several participants expressed support for the additivity approach as the "least unreasonable" or "most defensible" method, especially if it is used to establish a relative ranking of risks for a number of sites (Hattis, O'Flaherty, Clarkson, Durkin). Drs. O'Flaherty and Durkin pointed out that this approach is the most conservative in that it yields the largest estimated risk. Dr. Schneiderman accepted the additivity approach as an interim solution and suggested that for cancer effects the summation be limited to cancers at the same site or in tissues that have a similar embryonic origin. Other participants cited inadequacies of using an additive method including its failure to account for possibly large interactive effects (Withey) and multiple tumors resulting from exposures to carcinogens (Bingham, Suter). Dr. Hartung advocated more research into interactions between chemicals at low doses and chronic exposures, and Dr. Silbergeld suggested that the Agency may be better off in some instances by basing the assessment on a single chemical, i.e., dioxin.

2.5.3. Consensus. No consensus was clearly articulated on this topic, although a number of participants felt that the additivity method was an adequate interim approach. Two recommendations were made to the Agency:

1. Collect more data on chemical interactions, especially at low doses and chronic exposures, to better define the additivity model.
2. Consider that the application of the hazard index approach be limited only to chemicals or classes of chemicals causing a similar effect.

3. PRESENTATION OF NEW TOPICS (Session II)

3.1. APPROACHES USING STRUCTURE-ACTIVITY RELATIONSHIPS

3.1.1. Presentation (R. Bruins, K. Enslein, S. Broderius). Current U.S. EPA methods for estimating toxicant effect levels in humans depend upon the availability of data, however limited, on mammalian toxicity. The principle of analogy, where untested members of a chemical class are treated identically to tested members, has also been used but has been criticized as oversimplified. In this session, the use of structure-activity relationships (SARs) to estimate effect levels (i.e., NOAELs) and endpoints (i.e., cancer) for untested chemicals was discussed. Presentations described the use of equations based on substructural fragment descriptors in the prediction of various effects and the use of physicochemical properties to predict aquatic toxicity. Participants were asked to consider the potential applicability of these approaches to the overall risk assessment methodology. Aspects of particular importance are the amount of information needed to implement such an approach, and the reliability of the result in terms of accuracy (how well it works) and biological rationale (why it works).

Dr. Enslein presented an overview of the development and application of SARs to risk assessment. He defined the approach as an attempt through statistical modeling to explain or model biological responses with equations using parameters that describe known structures and their biologic activity. Historically, SAR has been used to optimize desired characteristics of pharmaceuticals and pesticides or to elucidate mechanisms of action of closely related chemicals. Two general approaches are used in SAR. The

first uses molecular orbital calculations to precisely describe the structure of the chemicals; in the second, empirical equations are derived using parameters that generally describe a substance's chemical and physical properties. In the second approach, the usual equation has the following form:

$$\text{Biological response} = \text{Constant} + (\text{Coefficient}_1 \times \text{Parameter}_1) + (\text{Coefficient}_2 \times \text{Parameter}_2) \dots + (\text{Coefficient}_n \times \text{Parameter}_n)$$

The parameters are octanol/water partition coefficients, electronic constants, indicator variables, substructures, and other physical parameters. Ideally, one would wish to develop equations for a series of related chemicals; however, few series have sufficient data, one of which is the polycyclic aromatic hydrocarbons. Dr. Enslein also cited some data on the performance of the equations he has developed for identifying mutagens, carcinogens, and teratogens (Table 3-1). He pointed out that the performance tests were not conducted with independent data; i.e., some or all of the data were used in the development of the equations. He also noted that the effect of the size of the database on equation performance was tested for the rat oral LD₅₀ equation; increasing the database from 1500 to 2000 chemicals did not improve the equation's performance. Finally, Dr. Enslein reviewed disadvantages in the SAR approach. The toxicological activity for only 60-90% of compounds can be estimated because the remainder have unique nondescribable structures or do not have sufficient data on the parameters used in the equations. In addition, all discriminant analyses have a gray area in which no conclusion can be made from the discriminant value (Dr. Enslein arbitrarily identifies values of 0.3-0.7 as indeterminate). Also, SAR is not currently applicable to mixtures and needs more verification to increase its credibility.

TABLE 3-1
Performance of SAR Equations

Toxic Endpoint	Number of Compounds Tested	False Positive (%)	False Negatives (%)	Accuracy (%)
Mutagenicity	472	5	5	90
Carcinogenicity	334	6	4	90
Teratogenicity	430	5	7	89

The second presentation was made by Dr. Broderius, who discussed the development of SAR at the EPA Environmental Research Laboratory (Duluth) and his research into the joint action of multiple organic toxicants. The initial SAR work involved the calculation of bioconcentration factors in aquatic animals for a variety of organic chemicals from one parameter, log P (the octanol/water partition coefficient). The results, from ~120 compounds tested in trout, showed a linear relationship between log P and bioconcentration; however, predictions made for compounds not used in the initial modeling were accurate only within 1 order of magnitude.

A second phase of the work was to develop models to predict acute toxicity of industrial compounds to aquatic organisms based primarily on two parameters, log P and water solubility. Approximately 200-300 compounds including organic solvents, ethers, and chlorinated benzenes were used to construct and verify the models. The results were that these compounds could be grouped into three classes that could be modeled with varying success. Compounds of low toxicity, which were also termed "nonspecific" toxicants because their primary effect was narcosis ("a reversible state of arrested activity of various protoplasmic structures"), fit the model well, showing good correlation between toxicity and log P and solubility. Compounds of moderate toxicity showed some correlation, and highly toxic and specific compounds had toxicities that showed little relationship to the modeling parameters.

Dr. Broderius also presented his research into the joint action of multiple toxicants in aquatic species, primarily the fathead minnow. He stated he has limited his study to strictly additive joint action as

initially described by Bliss and others. Using various binary combinations of ketones, such as 2-octanone and acetophenone, and alkyl alcohols, he found that these compounds displayed concentration addition in their effects. Other compounds, such as 2,4-pentanedione, 2-chloroethanol, and benzaldehyde, did not show additive effects when tested in combination with previously tested chemicals, and thus it was proposed they had different modes of acutely toxic action.

3.1.3. Discussion. Dr. Hartung noted that although SAR can be useful, some compounds are not suitable for the SAR approach and cited as an example the fluoro acids, which interfere with intermediate metabolism. In general, he felt that SAR is not applicable to compounds that are similar to biologically active materials, i.e., compounds that play a role in cellular physiology. Dr. Enslein responded that once a mechanism of action is known for a toxicant, an SAR evaluation can be developed. Dr. Stara stated that, if a mechanism of action were known, SAR would probably not be needed to conduct a risk assessment.

Three participants commented on the presentations of Enslein and Broderius in their postmeeting memoranda. Drs. Durkin and Silbergeld noted that the research presented by Dr. Broderius indicated that his SAR models worked best for compounds of low toxicity and that these compounds were of least interest for regulation and human risk assessment. Dr. Schneiderman

stated that SAR holds promise and raised the following questions and suggestions in regard to the Enslein SAR approach:

1. In the discriminant equation, what parameters contribute most to separating materials later labeled as carcinogens from those labeled noncarcinogens? Are these parameters different for different classes of chemicals? If so, how are classes of chemicals defined, or determined in advance?
2. What kind of self-learning process is built into the Enslein procedure? How have the parameters changed with additional data? How are missing data handled?
3. If comparisons of Enslein equations with other SAR approaches and with such testing procedures as short-term mutagenesis tests were made, these comparisons would (or should) include a proposal for stepwise testing (evaluation) of potential carcinogens. Can the Enslein process be set up with cutoff points to identify compounds that we can be sure will not be carcinogens? Dr. Schneiderman noted that, if this could be done, a great deal of testing might be eliminated.
4. Is there some way of adding electrophile information to the existing Enslein equations? If done, does it improve the discrimination?

3.2. USE OF REPRODUCTIVE EFFECTS AS ENDPOINTS IN RISK ASSESSMENT

3.2.1. Presentation (J. Stara, J. Manson). ECAO is faced with the question of how appropriately to use fetotoxic, teratogenic, and, in general, reproductive effect data in human health risk assessment. Although such data are limited, they need to be evaluated and considered in the estimation of potential hazard. Much additional basic and applied research must be done to provide a satisfactory data base for these purposes. Furthermore, the extrapolation process using reproductive effects is complicated because of species differences that may include different placentae, placental transfer rates, neonatal developmental stages, and lengths of pregnancy among others.

Dr. Manson introduced her presentation by stating that, at present, there is little experimentally based guidance for the use of reproductive or prenatal toxicity endpoints in risk assessment. In addition, she said a wide range of endpoints is possible as a result of a single exposure to a teratogen during development. To illustrate her points, Dr. Manson presented data on two teratogens that act through very different mechanisms. The first, methyl-N-nitro-N-nitroguanidine, is a direct-acting alkylating agent that specifically kills S-phase, or rapidly proliferating cells and, as a result, induces limb malformation. Her research found that this agent has a very narrow range of doses that will produce a doubling or tripling of effect and hence manifests a sharp demarcation between doses causing malformation and those causing fetal death. In addition, the unique pattern of limb deformation caused by the chemical was found to be a consequence of slightly different rates of cell proliferation in the limbs of one side of the fetus and that there was a very small "window" (~3 hours) during which exposure would cause the pattern of limb malformation. Furthermore, the distribution of the compound in the fetus had relatively little to do with the ultimate malformation or initial cellular toxicity. Dr. Manson concluded that for this type of direct-acting chemical, which is typical of almost all research drugs that have been studied in teratology, the final pattern of malformation depends more on the specific location of susceptible sites, i.e., the sites of the cellular replication, than on the chemical itself.

The second teratogen presented as an example was nitrofen, a herbicide that has little toxicity in the adult animal. Dr. Manson's research found that, unlike methyl-N-nitro-N-nitroguanidine, nitrofen has a unique mechanism of action in that it acts as a thyroid hormone analog. In addition,

she pointed out that although the kidneys of the exposed offspring were grossly malformed, kidney function was normal up to 100 days of age, thus raising the question of how to choose an endpoint in risk assessment for teratogens. Her conclusion was that it is unlikely that a general approach to the assessment of risk for teratogens could be developed and that each compound should be assessed individually. In addition, she said her work indicated the importance of performing thorough qualitative studies and identifying an appropriate toxic endpoint before attempting quantitative extrapolation to humans.

3.2.2. Discussion. Dr. Manson began the discussion by stating that in her opinion teratogens are a very rare type of toxicant. Dr. Silbergeld suggested that it was possible that more chemicals may be considered teratogens if one studied subtle detrimental effects on the central nervous system (CNS) resulting from prenatal exposure. Dr. Manson said that there is probably no chemical that acts only on the CNS. Dr. Legator proposed that it is possible that the wide divergence in gross morphologic effects resulting from teratogens in different species may actually stem from a common mode of action that occurs in the very early stages of development. Dr. Nelson agreed with this suggestion and asked Dr. Manson what teratogenic effects may occur at very low exposure levels. She said that there is no easy way to identify such effects.

Dr. Calabrese raised the question of using rodents for test species, since studies have indicated that they are more sensitive to teratogens than are humans. Dr. Clarkson stated that for methyl mercury, humans were the most sensitive. Dr. Calabrese said the difference between methyl mercury

and other teratogens may be due to difference in bioactivation and then asked Dr. Manson if teratogens, in general, had thresholds below which no effect occurred. She replied that there were insufficient data for a conclusion but that it was her belief that teratogens had thresholds. Dr. Withey noted that his studies of the pharmacokinetics of teratogens led him to question the term "dose" in teratology because he had found that some lipid-soluble compounds, which one would suspect would cross the placenta easily, did not. Dr. Hartung also noted that the exposure patterns used in teratology studies rarely duplicate human exposure.

In their postmeeting memoranda, Drs. Schneiderman and Silbergeld noted the need for the consideration of a broader range of effects than teratogenicity in the development of a policy in this much-neglected area. Dr. Silbergeld cited fetotoxins and gonadal toxins as candidates for regulation, and Dr. Schneiderman mentioned pregnancy wastage and reduced fertility as possible endpoints. He also cited three steps that are currently possible in the development of a policy:

1. Establishment of a minimum number of endpoints to be studied.
2. Creation of a database on spontaneous abortions in humans.
3. Promotion of studies of effects of some toxicants on germ cells in whole animals.

3.3. USE AND BIOLOGICAL JUSTIFICATION OF MATHEMATICAL MODELS

3.3.1. Presentation (R. Hertzberg, E. O'Flaherty). Several models and calculation schemes have been adopted or proposed for use in predictive health risk assessment. Among these are additivity of risk and dose,

species conversion by dose per body weight, time-weighted averaging for any dose rate, and route equivalence using the Stokinger-Woodward formula. These calculation methods must be evaluated for possible errors based on known biological mechanisms, behavior, or numerical methods.

In his presentation, Dr. Hertzberg discussed the general principles underlying the development of a mathematical model of a biological process and pointed out that most models used in toxicologic risk assessment may benefit from a reexamination of their assumptions and validity. He divided the model building process into three steps: 1) development of a mathematical and theoretical description of a given biological system or process, 2) calibration of the model with a broad range of applicable data, and 3) verification and validation of the model with a second set of data. He also stated that it is important to carry through the model's assumptions to the final calculation to prevent overinterpretation of the model's predictions. As an example of this process, Dr. Hertzberg proposed a simple model to justify the surface area approach to interspecies dose conversion. He outlined three assumptions: the dose at the target tissue determines the toxic effects; the function and anatomy of organs are similar for mammalian species; and, in this case, metabolism detoxifies the toxicant. He also discussed the implications of these assumptions for the final form of the model. As a second example, Dr. Hertzberg described an approach for estimating a cleanup level based on known prior exposures. He pointed out that the initial curve used by the ECAO, an ADI line based on the results of laboratory experiments utilizing continuous exposures, does not represent the exposure pattern of humans in which exposures decrease after a site is

cleaned up. Hence, the question is whether the total human exposure constitutes an acceptable level: how can one choose a post-cleanup level that, in light of previous exposures, will be safe? One approach is to require that the time-weighted average for any time after cleanup be acceptable, that is, assure that the average human exposure duplicates the laboratory situation.

Dr. O'Flaherty focused her talk on one aspect of route-to-route extrapolation, first-pass effects. The text of her talk follows.

"The purpose of this presentation was to illustrate several important features of first-pass metabolism that must be taken into account by pharmacokinetic or toxicokinetic models. These features have direct relevance to issues surrounding route-to-route extrapolation.

"The first point made was that the lung should not be too readily dismissed as a metabolizing organ. Although it is true that the total metabolizing capacity of the lung is much less than that of the liver, there are circumstances under which metabolism in the lung may be a significant fraction of total metabolism. An example is shown in the Table 3-2 taken from a paper by Roth and Wiersma (1979). It shows the predicted clearance of benzo(a)pyrene (BP) in the lung and liver of control ("basal") rats and of rats pretreated with 3-methylcholanthrene [3-MC] to induce BP metabolism. The predictions were made by incorporating experimentally measured metabolic capacities and physiologically reasonable blood flow rates into a simple and generally accepted model of organ clearance.

"It is apparent from the table that although pulmonary metabolism of BP in non-pretreated rats is only 0.4 percent of hepatic metabolism, in 3-MC treated rats the predicted BP metabolizing activity of the lung is 60 percent that of the liver. The reason is not differential induction, since metabolizing capacity was induced to the same extent in both organs. The explanation for the increased relative importance of the lung in metabolism

TABLE 3-2

Predicted Clearance of Benzo(a)pyrene in Rats*

Organ	Blood Flow (ml/minutes)	Predicted Clearance (ml/minutes)	
		Basal	3-MC induced
Lungs	44.8	0.027	6.64
Liver	11.2	6.08	11.0
Lungs/liver	4.0	0.004	0.60

*Source: Roth and Wiersma, 1979

of BP in 3-MC treated rats is that liver metabolism has become perfusion-rate-limited while lung metabolism remains capacity-limited, so that the full effect of induction is observable in the lung but not the liver.

"This distinction between perfusion-limited and capacity-limited metabolism is fundamental to an understanding of first-pass metabolism. The total metabolic capacity of an organ is related to a useful parameter, intrinsic clearance or CL_{int} , which is expressed in units of ml/min and, thus, is the counterpart of organ perfusion rate, Q . The first-pass metabolic behavior of a compound presented to the liver is determined by the relative magnitudes of $CL_{int,L}$ and Q_L where the subscript L designates the liver. Either perfusion rate Q_L or intrinsic clearance $CL_{int,L}$ can be rate-limiting.

"If $CL_{int,L}$ is much less than Q_L , metabolism is rate-limiting at all or nearly all doses. Saturation of hepatic metabolizing enzymes will occur at low doses. First-pass metabolism will be insignificant, and dose dependence of first-pass metabolism undetectable. But because of the small value of $CL_{int,L}$, systemic half-life $t_{1/2}$ will be dose dependent. Diphenylhydantoin is an example of a compound in this class. It is at least 98 percent bioavailable at all doses (Jusko et al., 1976). However, its systemic $t_{1/2}$ is dose dependent even at doses within the therapeutic range.

"Induction of metabolism of compounds for which $CL_{int,L}$ is much less than Q_L will shorten the systemic $t_{1/2}$ but have an insignificant effect on bioavailability.

"If $CL_{int,L}$ is much greater than Q_L , perfusion is rate-limiting. Bioavailability from an oral dose will be low, and in fact may be 0 at low doses. But because virtually all of an intestinally absorbed dose reaches the liver on the first pass, the rate of presentation of absorbed compound to liver enzymes may exceed the maximum rate at which the compound can be metabolized, even at intermediate doses and certainly at high doses. Thus, the magnitude of the first-pass effect will be both large and dose dependent. On the other hand, because of the large value of $CL_{int,L}$, systemic $t_{1/2}$ will not be dose dependent. Phenacetin is one such compound. Its

bioavailability from a 250-mg dose was zero in six human subjects and from a 1-g dose was 0-49 percent in four human subjects. But its systemic $t_{1/2}$ was 37-74 minutes in all subjects, independent of dose (Raaflaub and Dubach, 1975).

"Induction of metabolism of compounds for which $CL_{int,H}$ is much greater than Q_L will reduce bioavailability further but will have no effect on systemic $t_{1/2}$.

"These examples represent the extremes. There is a range of intermediate relationships of Q_L to $CL_{int,L}$ in which both systemic $t_{1/2}$ and bioavailability may be affected by dose and by the animal's status with regard to enzyme induction.

"Five consequences of first-pass metabolism were pointed out. These are:

1. First-pass metabolism alters the relationship between applied dose and internal dose. Figure 3-1 illustrates this point.
2. First-pass metabolism leads to the earlier appearance of larger amounts of metabolite in the circulation, so that both metabolite peak height and total exposure to metabolite are increased. Figure 3-2 illustrates this point.
3. If the metabolite is active, plasma levels of the parent associated with a given magnitude of effect will be lower after oral than after inhalation exposure.
4. If metabolites are associated with a spectrum of effects different from the effects associated with the parent, dose dependence of first-pass metabolism could be responsible for dose dependence of the nature as well as the magnitude of the effect.
5. Provided that metabolism is a major route of elimination, compounds for which $CL_{int,L}$ is large will have a short systemic $t_{1/2}$ and will undergo a large first-pass effect. On both these counts, they are poor candidates for route-to-route extrapolation procedures. Compounds for which $CL_{int,L}$ is small will have a long systemic $t_{1/2}$ and will undergo only a small first-pass effect. On both these counts, they are good candidates for route-to-route extrapolation procedures."

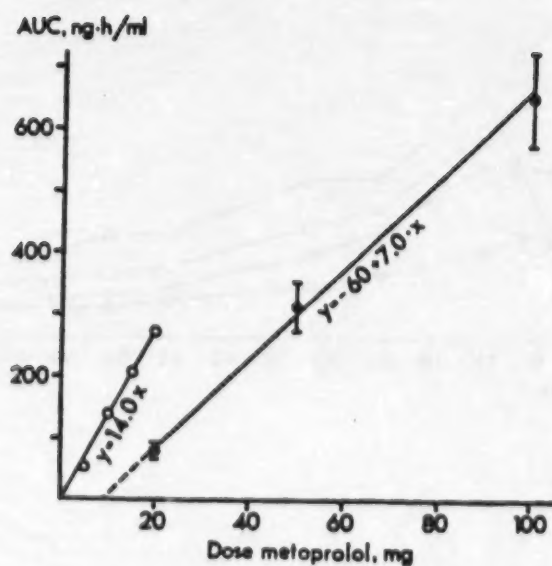


FIGURE 3-1

The relationship between a measure of internal dose, the area under the concentration, time curve (AUC), and either oral (○) or intravenous (●) metoprolol dose in five male human subjects. Note that the metoprolol is 0% bioavailable from low oral doses

Source: Johnsson et al., 1975

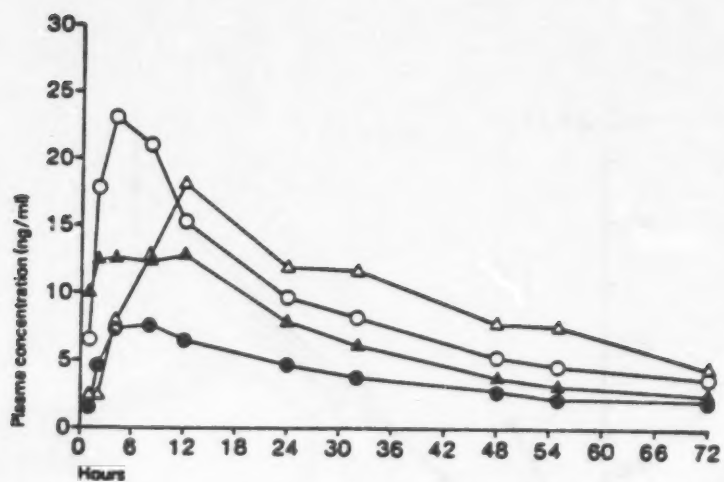


FIGURE 3-2

Mean plasma concentrations of nortriptyline (solid symbols) and its major metabolite, 10-hydroxynortriptyline (open symbols), after oral (O,●) and intramuscular (Δ,▲) administration to six patients

Source: Alvan et al., 1977

3.3.2. Discussion. Several participants commented on Dr. Hertzberg's presentation, noting that the initial assumptions in the dose conversion example may not be completely accurate or comprehensive (Nelson, Clarkson). Dr. Hartung said that at a higher level of sophistication, the model suggests that organ weight should be considered in the conversion; however, Dr. Silbergeld noted that the organ with the highest level of toxicant is not necessarily the most affected organ. Dr. Withey also commented on this approach by pointing out that Gillette (1976) has developed a procedure in which the rate processes for each metabolite are evaluated to find the concentration of the active molecule at the target site. Dr. Andelman commented on the example for estimating ADIs for people near sites that had been cleaned up and stated that it is important to know the age distribution of the exposed population to determine in what way ending exposures at different ages may influence the estimated ADIs.

In her postmeeting memorandum, Dr. Silbergeld noted that the model presented by Dr. Hertzberg could be improved by the consideration of Michaelis-Menten type kinetics and suggested that a model for procarcinogens (Hoel, 1983) be reviewed as a useful example. Dr. Schneiderman noted the need for developing models of diseases other than cancer. He also wrote that response models as well as dose models need to be considered and that, in general, the effects of peak doses vs. the effect of cumulative doses, population variability, and tissue-specificity problems (i.e., first-pass effects) need to be considered in constructing biologically based models.

4. WORKSHOPS (Session III)

The participants were assigned to four workshop groups as listed below. The charge to each workshop was to discuss the topic, develop a statement describing the state of the art, and recommend a course of action that could be taken at this time.

WORKSHOP TOPIC

A1 Sensitive Subgroups

Bingham (Chairperson)	Legator	Piscator
Calabrese	Manson	Schneiderman
Enslein	Nicholson	Silbergeld
Hattis	Nisbet	

B1 Multiple Route Exposure

Albert	Crump	Nelson (Chairperson)
Andelman	Durkin	O'Flaherty
Clarkson	Hartung	Withey
Cornish	Mehlman	Wyzga

A2 Ranking Severity of Effects

Albert (Chairperson)	Hartung	Nelson
Bingham	Hattis	Nicholson
Calabrese	Legator	Piscator
Durkin	Manson	Schneiderman

B2 Use of Exposure Data in Assessing Health Risk

Andelman	Enslein	Silbergeld
Clarkson	Mehlman (Chairperson)	Withey
Cornish	Nisbet	Wyzga
Crump	O'Flaherty	

4.1. CONSIDERATION OF HIGH RISK (SENSITIVE) SUBGROUPS IN HEALTH RISK ASSESSMENT

4.1.1. Presentation (L.S. Erdreich, D. Hattis). The present U.S. EPA guidelines for calculating an ADI include a 10-fold uncertainty factor to account for intraspecies variability. This 10-fold factor has traditionally

been assumed to account for the "sensitive individual." This theoretically encompasses both interindividual variations of a normal healthy adult population and high risk subgroups. Some scientists believe that this factor will prove inadequate to protect high risk subgroups in the population who, because of predisposing factors, will be more sensitive to specific chemical insults. Predisposing factors include but are not limited to the following: developmental processes, age, nutritional deficiencies, disease states, genetic conditions, behavioral factors, and previous or concomitant exposures. It was the purpose of this workshop to consider this problem and to evaluate and devise methods that would allow for better incorporation of these uncertainties and differences into the risk assessment process. Two topics of discussion were presented: the first was an evaluation of the data needed to assess the variation in a population's response to toxicants, and the second was a rating scheme that would, at least qualitatively, weight risk assessments with regard to consideration of sensitive subgroups.

The initial discussion was centered around the data available for an assessment of the magnitude of the differences in individual responses to toxicants. Data from pharmacogenetic studies were presented and their use in such an assessment was discussed. The significant advantages in using such data include the following: 1) they are from studies of humans, 2) they describe the response to xenobiotics that have been given in measured doses to a group of individuals, and 3) in some instances, they are collected under conditions in which interindividual variability is controlled (i.e., monozygotic twins). Disadvantages in the use of pharmacogenetic data are that they generally show differences in a pharmacokinetic parameter instead of an adverse effect and they are derived primarily from studies of drugs rather than environmental toxicants.

Dr. Erdreich pointed out that there was a fairly large body of literature on studies that measure interindividual differences in a wide variety of parameters ranging from lung plutonium concentrations to the clearance and metabolism of a number of drugs. She suggested that collection and analysis of these data might be relevant for estimating the variance in response. A general consensus on this approach was reached and additional sources of information were suggested (Schneiderman, Silbergeld), such as registries of special diseases or conditions, the Fels Research Institute longitudinal study, special exposure groups (industrial, Love Canal), and perhaps retirement populations (the residents of Leisure World). The suggestion was also made that chemical-specific lists (cross indexed by effect and sensitive group) should also be established.

The second topic of this workshop considered an interim approach proposed by ECAO to address the problem of sensitive subgroups. This qualitative approach adjusts the number exposed to reflect the proportion of high risk (HR) individuals and weights the total hazard index by the size of the exposed population. The interim approach also provides information for comparing hazards among exposed populations.

The first steps of this procedure would be included as a part of the toxicity assessment (Figure 4-1) which summarizes the overall multichemical risk assessment process. The rating scheme itself is part of the integration of the toxicity and exposure assessments. The initial steps for considering sensitive subgroups are as follows:

1. Identify appropriate HR groups for the chemicals in question. These subgroups are to be selected from the general categories in Table 4-1, but are limited to well-defined HR groups of relatively high prevalence (>1%).

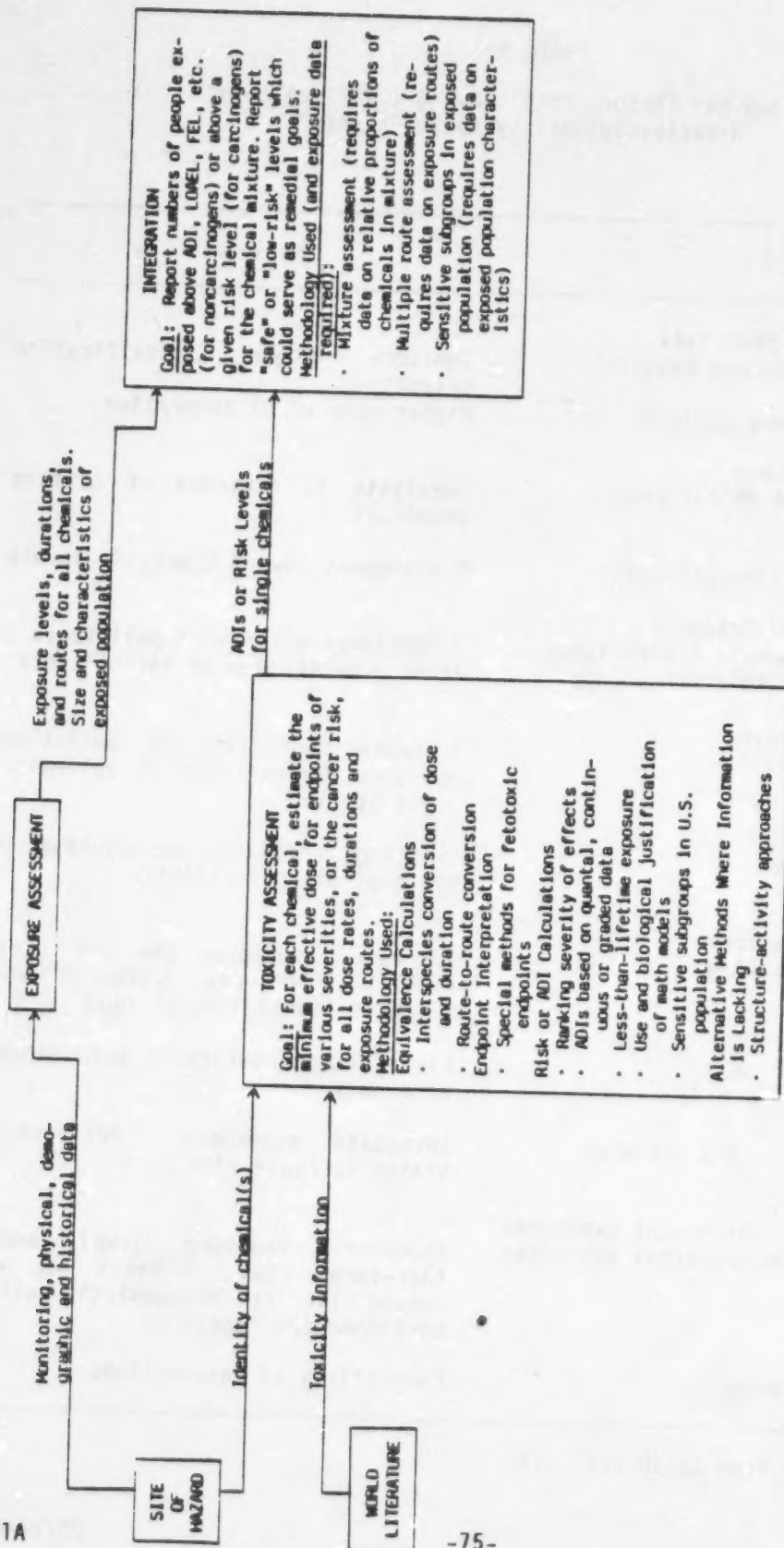


FIGURE 4-1

Information flow and methodology use in conducting site-specific multichemical health risk assessment, showing use of each methodology component under development by ECAO-Cincinnati

TABLE 4-1
Biological Factors Predisposing Individuals to
Hypersusceptibility to Pollutants*

Factors	Rationale
I Developmental Processes Examples: Pre- and Neonatal Young children	Immature enzyme detoxification systems Higher rate of GI absorption
II Genetic Disorders Examples: G-6 PD deficiency Sickle-cell trait	Hemolysis in presence of certain chemicals Predisposes toward hemolytic anemia
III Nutritional Deficiencies Examples: Vitamin C deficiency Protein deficiency	Potentiates effects of pollutants Affects metabolism of insecticides
IV Existing Disease Examples: Heart Lung	Increased mortality in pollution episodes demonstrated in epidemiologic studies Existing conditions are aggravated by respiratory irritants
V Behavioral Factors Examples: Smoking Alcohol Dietary patterns	Increases exposures and therefore risk: interferes with normal cleansing mechanisms of lung Liver damage, synergism with other chemicals Increases exposures: deficiency states increase risk
VI Previous or concomitant exposures Examples: Occupational exposures Drugs	Increases exposure level and, therefore, risk. Effects may be synergistic or antagonistic with environmental exposures Possibility of interactions

*Source: Adapted from Calabrese, 1978

2. Determine the prevalence of the HR groups in the general United States population or approximate subgroups (i.e., racial groups for certain genetic factors).
3. Incorporate this information into the rating scheme of the integrated risk assessment.

This interim approach was not too well received. Many of the criticisms leveled at it were summarized in the second presentation of the workshop, made by Dr. Hattis. His criticism was grouped into three areas:

1. The proposed approach assumes a discontinuous population subgroup model of "hypersusceptibility"; however much of the variability between individuals in susceptibility may appear as continuous because of a host of factors acting as quantitative characters, and not based on obviously discernible membership of people in discrete, countable subgroups.
2. The proposed approach appears to implicitly assume that the average hypersusceptible person is only about twice as susceptible as the average nonhypersusceptible person. (If the difference was actually this small, it wouldn't be significant amid the other uncertainties of quantitative risk assessment.)
3. The proposed restriction to hypersusceptible groups constituting at least 1% of the population, while it flows naturally from the proposed calculating method, is arbitrary and potentially seriously misleading. Consider, for example, a case where there exists a 0.1% subgroup that is ten thousand times as susceptible to a toxin as the average individual. Quantifying the size of the population that is very much more susceptible than average is the essence of a quantitative risk assessment for a threshold character with widely varying sensitivity.

Dr. Hattis suggested that, instead of the proposed approach that evaluates sensitive subpopulations on a chemical-by-chemical basis, a better approach would be to analyze the sources of variation in sensitivity, define acceptable methods for estimating the variability contributed by each source and then incorporate these estimates into a stochastic simulation model to compute the overall distribution of population sensitivity for the chemical.

He proposed three sources of variability:

1. Exposure is effectively more for a subgroup because of either biology or behavior.
2. Parameters determining normal/abnormal function are closer to (or even beyond) the boundary of abnormality for the subgroup (these groups have less "reserve capacity" so smaller insults would be required to exceed their ability to handle insults).
3. There are more parameter changes per unit of dose for a particular subgroup because of biological differences either in pharmacokinetic parameters (i.e., faster rate of absorption) the fraction of a chemical metabolized by "safe" or "dangerous" pathways or differences in the quality or quantity of receptors.

He further suggested that these three sources could be analyzed as follows:

1. Have a reasonably standardized analysis of susceptibility for the exposure-related factors, depending only on the routes of anticipated exposure of the target population.
2. Do a series of standard analyses of population variability for different well-characterized physiological functions that are affected by toxic agents (i.e., oxygen transport and nerve conduction). For substances that affect unknown physiological parameters, use a "typical" variability profile borrowed from one of the well-characterized functions for "best estimate" calculations, and some more extreme assumption of variability for "conservative" or "worst case" projections.
3. To the extent possible, analyze pharmacokinetic and receptor-related variability chemical by chemical. Where chemical-specific data are not available, it may often be necessary to adopt some general rules based on previous experience with specific chemical classes or chemicals affecting specific receptors.

The results from such an analysis could be entered into the stochastic model and used to estimate the overall susceptibility of a population to each chemical, with default values being used in the absence of actual information. The computer would then construct a synthetic population of

whatever size was desired and, according to the distribution of susceptibilities in these three categories, would simulate the size and extent of susceptibility.

4.1.2. Discussion. The discussion was opened by Dr. Bingham who asked the question, "Is it worth the effort to get something better than the 10-fold factor and, if so, then how do we go about it?" One response was that, before a different approach could be derived, the question of the types of effects to be considered important had to be addressed because it might not be necessary to have a 10-fold factor for all effects. Some may require a 100-fold factor, others a 2-fold factor. Dr. Nicholson then suggested that the utility of a 10-fold factor could be checked by looking at the range of probit slopes for dose-response curves occurring in the population.

Dr. Dourson then briefly discussed the current agency policy, which is to pick the "critical" effect (the adverse effect which occurs at the lowest dose), find the NOAEL for it, and apply a 10-fold factor. The rationale behind such an approach is that protecting against the "critical" effect should protect against all adverse effects. Unfortunately, this approach does not take into consideration the situation in which the log probit slopes for different effects are not parallel, such that an effect with a higher dose has a more shallow slope and results in a lower ADI than that based on the critical effect. This approach is predicated on threshold effects; it may not matter which effect is used as long as the ADI is below the threshold for all adverse effects. Dr. Legator then indicated that

thresholds for individuals have to be distinguished from population thresholds, and the question was raised by Dr. Calabrese of how superimposition of effects influences a 10-fold factor.

Dr. Nisbet pointed out some clear differences between children and adults who are exposed to toxic chemicals. Children (under 9) spend 4-8 times more time outdoors; they breathe 3-5 times more air per unit of body weight (bw); and they take in 3-4 times more food per unit of bw, 5 times more fluid, and 6 times more dairy products; breast-fed infants receive 10-20 times more lipid-soluble chemicals. Also, because children spend more time in contact with the soil and their skin is more permeable, it is estimated that they receive 5- to 10-fold more exposure than their parents. These differences are in addition to those differences that might be shown by pharmacogenetic information. Dr. Enslein also pointed out that there are also several large studies on populations with various disease states and that these might provide information as to variability.

Dr. Bingham closed the discussion by querying, "Should EPA come up with chemical specific lists of high risk groups?" Dr. Nisbet suggested that these be drawn up by groups of people and types of effects. The general consensus was that the scheme presented was inappropriate, and that evaluation of sensitive subgroups should be part of an ADI determination rather than the calculation of the hazard index.

4.1.3. Workshop Statement. Dr. Schneiderman prepared a statement on the conclusions reached by the workshop participants. He grouped the conclusions into the following three areas:

1. "One 'safety-factor' number (i.e., division by 10 or 100) is inadequate to take into account the variability in the human population. Safety factors developed for adults are inappropriate for use with children. Action: Develop needed data relating to safety factors for different segments of the population. In the interim use current factors, setting a deadline as to when they should be reconsidered.
2. "For future changes in safety factors, base safety factors on the following data:
 - a. Slope of the dose-response curves (the more shallow the slope, the larger the factor required).
 - b. The specific toxicity and its severity (the greater the need to protect against the toxicity, the larger the safety factor needs to be. A lifetime of illness or reduced functional ability is usually more important than a short-term, reversible incident).
3. "For noncancer effects, remain with the ADI concept, rather than a 'hazard index.' While the public-health consequences are greater when more people become ill (hazard index), it is individuals who become ill, and even a small number of persons are to be protected against serious consequences."

4.2. ASSESSMENT OF MULTIPLE ROUTE EXPOSURE

4.2.1. Presentation (W. Pepekko, R. Hartung). Under certain conditions humans are exposed to environmental pollutants by more than one route of exposure. The three major portals of entry include the lungs, GI tract, and skin. While it is possible to be exposed by other routes such as intravenous or intramuscular injection, the use of these routes is generally limited to treatment with therapeutic drugs or other nonenvironmental exposures.

Such routes were therefore not emphasized in the discussion. The skin has a much smaller surface area than the lungs and is generally less permeable to environmental pollutants. Under normal conditions of exposure to environmental pollutants, in which the concentrations are very low, entry through the skin will add very little to body burdens. Thus, in most cases, it should be necessary to consider only two routes of exposure, inhalation and intragastric.

The major issue to be resolved was whether exposures by more than one route should be summed, and if so, how? It was proposed that summation is not valid under the following conditions:

1. A significant amount of pollutant is absorbed by only one route.
2. The pollutant chemical is completely removed or inactivated before reaching the target organ (i.e., first-pass effect for liver), except for one route.
3. The portal of entry is the primary target organ. This brings up two questions to be considered. If the target organ is different for each route of exposure, should the situation be treated as two different chemicals with two separate ADIs? In such cases will exposure by one route (at above threshold levels) affect the threshold for exposure by another route?

If none of the conditions listed above is present, then it is proposed that summation of the exposures by more than one route can be done. At the previous meeting, a mathematical approach was proposed for this summation:

$$d_n = d_1 r_1 + d_2 r_2 + \dots d_i r_i$$

where d_n = total dose, d_i = the various exposure routes, and r_i = the absorption fraction for each exposure route; d_n is then compared with the ADI.

The previous equation is simple, straightforward, and easy to apply. It should be possible to apply this equation successfully in cases where the target tissue is the same for each route of exposure, where the elimination half-time is sufficiently long so that the route of exposure will not affect temporal target organ concentration relationships, and where the absorption coefficient is known for each route of exposure.

The more difficult cases and the ones that were to be emphasized at this workshop are those in which a straightforward summation of d_{1r_1} is not possible. These include the following examples:

1. The target organs are generally different for two exposure routes but not exclusively so.
2. Partial removal of an absorbed dose occurs following exposure by one route but not another.
3. As a result of short elimination, the half-time target organ concentrations fluctuate during intermittent oral dosing as compared with constant levels during inhalation exposure.

Under these conditions, can absorbed doses by different routes be summed with any degree of accuracy, and if so, how?

Dr. Hartung summarized his presentation in his postmeeting memorandum. The portion relevant to this workshop is as follows:

"Multiple-Route Exposure: The evaluation of multiple route exposures was analyzed as a special case of route:route extrapolation, and in the case when exposures by different routes produced different effects as a special case of multichemical exposure. The simplistic additive approach suggested earlier, and as summarized in the premeeting information, was considered to be inadequate.

"The approach taken to the problem was to consider first those conditions under which a multiroute exposure evaluation could be made with confidence. In order to keep the problem tractable, the problem analysis was considered for a single species only. An evaluation with confidence can be made if and only if all of the following conditions are met:

- "1. The dose-duration of exposure patterns are identical for all routes of exposure;
- "2. The systemic effects are identical for all routes of exposure;
- "3. No route-specific effects are found at the portal of entry;
- "4. There are no first-pass effects; and
- "5. The dose-duration of exposure-response surface is known in terms of absorbed dose (or, the relationships between applied dose and absorbed dose are known for each route).

"Points 1 and 4 are likely to become unimportant if the chemical is cleared very slowly from the body.

"If all of these conditions are met, then the total absorbed dose could be estimated, and subsequently the systemic response in terms of absorbed dose could be evaluated.

"It was recognized that these preconditions would only rarely, if ever, be met for a specific compound. It was also pointed out, that as these various preconditions are violated, then the ability to predict the consequences of exposures by various routes deteriorates in ways that are not easily predictable.

"If there were route-specific effects, then a simple summation of absorbed doses would probably be misleading, since interactions between

effects would not be taken into account appropriately. Under such conditions (if dose/response relationships were known for each route of exposure), the problem could be treated as a special case of the simple joint action additivity model as postulated by Bliss (1939). Such a model could readily be formulated in terms of external dose, rather than absorbed dose.

"Since exposures by multiple routes appear to be common, and since dose/response information is often imperfectly known for the various routes of exposure, it is tempting to attempt estimations of the effects of multiroute exposures on the basis of mixtures of chronic and acute data or on the basis of chronic data alone. Such estimates may be very unreliable and misleading."

4.2.2. Discussion. Several participants commented on the limitations to the general approach outlined by Dr. Hartung, including the likelihood that some chemicals produce overlapping effects through different routes (Albert), that environmental exposures are at low doses and effects are likely to be subtle (Nelson), and that the largest database for preparing dose-response curves is for acute exposures (Durkin). Dr. Nelson stated that, in addition to the proposed approach, the risk assessor should be aware of the limitations in the data and proposed a four-tier system, with the highest tier corresponding to the highest level of confidence in the assessment and the lowest tier, to the lowest level of confidence. The four tiers are as follows:

1. All of the necessary information is available, including dose/response/time curves for all three routes.
2. Information is available on two routes, and the remaining information is available through experimentation to determine absorption coefficients, internal doses, and body burden data.

3. Acute data are available for all three routes, and chronic data are available for one.
4. Acute (and chronic) data are available for only one route.

As a practical approach, for a single situation one could identify which of Dr. Hartung's preconditions were met or were not pertinent and then gauge the level of confidence in the assessment (Nelson). Dr. Albert pointed out that the assessment of multiple exposures is sufficiently complex that no one simplistic approach is adequate, and recommended a case-by-case approach using the available data. Dr. Durkin noted that specifying a minimum amount of data without which an assessment would not be performed is a necessity.

In her postmeeting memorandum, Dr. O'Flaherty noted that the characteristics of few compounds will be known in sufficient detail to meet Dr. Hartung's five criteria for an ideal candidate and to allow summation across routes. Therefore, she proposed the following generalizations on the extent to which some compounds may meet the criteria:

- "1. Internal dose-duration patterns are likely not to differ significantly across routes of exposure if the chemical has a long $t_{1/2}$. Concentration cycling around the mean steady-state blood concentration is damped if the compound has a long $t_{1/2}$, so that for such compounds the difference between dose-duration patterns for intermittent-exposure routes and for continuous exposure routes is minimized. Alternatively, even for compounds with short $t_{1/2}$, if patterns of exposure are roughly comparable the internal dose-duration patterns may also be roughly comparable. For example, exposure through water, although discontinuous, would fall somewhere between continuous exposure by inhalation and administration of the same total daily dose to an animal by single gavage.
- "2. Although situations in which systemic effects are different for different routes of administration can readily be imagined, we were unable to identify any compounds for which this is true. It may be possible to infer that few chemicals do not meet this criterion.

- "3. Highly chemically reactive compounds, or compounds with long residence times in the tissue of entry, should be suspect with regard to their potential for causing portal-of-entry effects. However, it cannot be assumed that compounds that are not highly reactive or have short residence times in the tissue of entry will not cause portal-of-entry effects.
- "4. Compounds with long $t_{1/2}$ are less likely to undergo significant first-pass effects than are compounds with short $t_{1/2}$. Thus, as a result of both considerations 1 and 4, it appears that compounds with long $t_{1/2}$ may be suitable candidates for summation across exposure routes."

4.2.3. Workshop Statement. The essential points of the workshop were agreed upon by Drs. Nelson, Clarkson, and Pepelko. Dr. Hartung's five conditions for conducting an assessment of a multiroute exposure were considered a valid starting point against which other approaches should be evaluated. The limitations in the available data are likely to preclude meaningful assessments at the present time, although some gauge of the level of confidence in an assessment is possible and desirable.

4.3. RANKING THE SEVERITY OF EFFECTS

4.3.1. Presentation (M. Dourson, P. Durkin). In this workshop, a scheme was presented for ranking potential adverse effects from chronic exposures, which is to be used for identifying reportable quantities (RQs) as required by CERCLA. This act stipulates that once a spill occurs resulting in the release of a hazardous material in a quantity greater than the RQ, the spill must be reported to the Agency. Under Section 102(b) of the act, the RQ of any hazardous substance is 1 pound, unless a different RQ has been established; statutory RQs can be set at 1, 10, 100, 1000 or 5000 pounds. The current regulatory approach uses six primary criteria for setting an RQ: aquatic toxicity, mammalian toxicity (acute), ignitability, reactivity,

other toxic effects (chronic), and carcinogenicity. For each criterion, a five-tiered rating scale is set up corresponding with the RQ values of 1, 10, 100, 1000 and 5000 pounds. There are also three secondary criteria (biodegradability, hydrolysis, and photolysis) that may adjust the RQ up by one level.

In the scheme presented at the workshop, determination of a reportable quantity based on chronic toxic effects requires a composite score (CS), which is the product of a rating value for dose (RV_d) and a rating value for effect (RV_e). Each RV can vary from 1 to 10; hence, the CS varies from 1 to 100. The higher the CS, the lower the RQ.

The following is a brief description of the calculation of an RQ. First, an RV_d is derived as follows for each route of exposure for which there are data:

1. Identify subchronic or chronic NOAELs, LOAELs or FELs.
2. Convert above dose to units of mg/kg/day.
3. If above dose is based on subchronic exposure, divide by 10.
4. Estimate a minimum effect dose (MED) for humans by converting above dose using surface area conversion.
5. Assign a rating value to MED as shown in Figure 4-2. This is the RV_d .

The RV_e that is associated with the MED is derived as shown in Table 4-2.

The RQ is then assigned on the basis of the following relationship (Table 4-3) using the highest composite score (the product of RV_d and RV_e for each route of exposure).

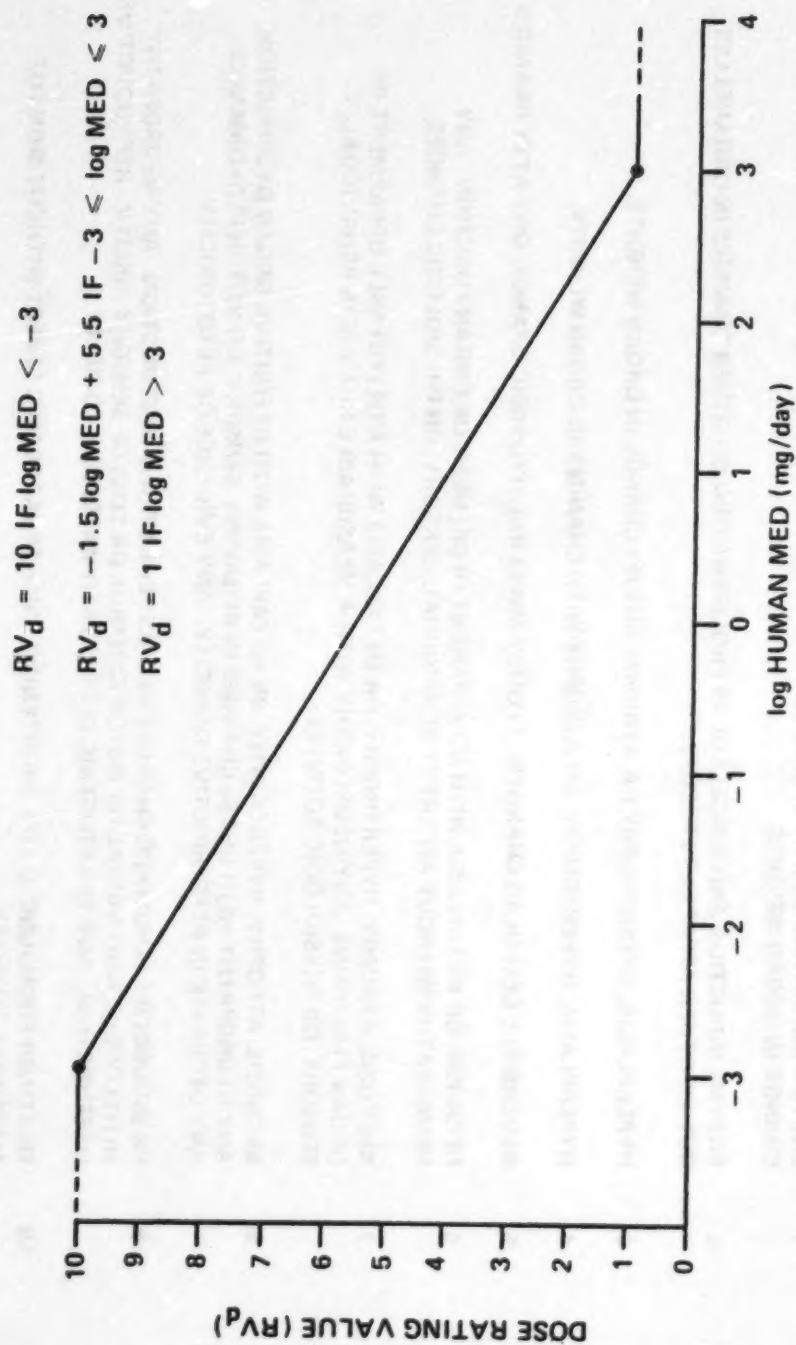


FIGURE 4-2
Rating Values for Doses

TABLE 4-2

Rating Values for NOELs, LOAELs and FELs for the Determination of RV_e

RATING	EFFECT
1	ENZYME INDUCTION OR OTHER BIOCHEMICAL CHANGE WITH NO PATHOLOGIC CHANGES AND NO CHANGE IN ORGAN WEIGHTS.
2	ENZYME INDUCTION AND SUBCELLULAR PROLIFERATION OR OTHER CHANGES IN ORGANELLES BUT NO OTHER APPARENT EFFECTS.
3	HYPERPLASIA, HYPERTROPHY OR ATROPHY BUT NO CHANGE IN ORGAN WEIGHTS.
4	HYPERPLASIA, HYPERTROPHY, OR ATROPHY WITH CHANGES IN ORGAN WEIGHTS.
5	REVERSIBLE CELLULAR CHANGES: CLOUDY SWELLING, HYDROPIC CHANGE, OR FATTY CHANGES.
6	NECROSIS, OR METAPLASIA WITH NO APPARENT DECREMENT OF ORGAN FUNCTION. ANY NEUROPATHY WITHOUT APPARENT BEHAVIORAL, SENSORY, OR PHYSIOLOGIC CHANGES.
7	NECROSIS, ATROPHY, HYPERTROPHY, OR METAPLASIA WITH A DETECTABLE DECREMENT OF ORGAN FUNCTIONS. ANY NEUROPATHY WITH A MEASURABLE CHANGE IN BEHAVIORAL, SENSORY, OR PHYSIOLOGIC ACTIVITY.
8	NECROSIS, ATROPHY, HYPERTROPHY, OR METAPLASIA WITH DEFINITIVE ORGAN DYSFUNCTION, ANY NEUROPATHY WITH GROSS CHANGES IN BEHAVIOR, SENSORY, OR MOTOR PERFORMANCE. ANY DECREASE IN REPRODUCTIVE CAPACITY. ANY EVIDENCE OF FETOTOXICITY.
9	PRONOUNCED PATHOLOGIC CHANGES WITH SEVERE ORGAN DYSFUNCTION. ANY NEUROPATHY WITH LOSS OF BEHAVIORAL OR MOTOR CONTROL OR LOSS OF SENSORY ABILITY. REPRODUCTIVE DYSFUNCTION. ANY TERATOGENIC EFFECT WITH MATERNAL TOXICITY.
10	DEATH OR PRONOUNCED LIFE SHORTENING. ANY TERATOGENIC EFFECT WITHOUT SIGNS OF MATERNAL TOXICITY.

TABLE 4-3

Relationship of Composite Score to RQ

Composite Score	RQ
81-100	1
41-80	10
21-40	100
6-20	1000
1-5	5000

4.3.2. Discussion. Several issues were raised during the discussion and in postmeeting memoranda. Dr. Albert defined three questions that he thought the participants should address relative to the proposed schemes:

1. Do the participants agree with the rating for toxicity in Table 4-2?
2. Do the participants agree with the rating proposed for dose, and if so, should it essentially be a log function?
3. Do participants agree with the multiplicative approach for combining the two rating schemes?

With regard to the first question, Dr. Stara asked if the group (or possibly the National Academy of Sciences) should be asked to develop a catalog of effects to better define the toxicity rating and to provide input as to where FELs, LOAELs, and NOAELs fall in the rating scheme. Dr. Hartung suggested that perhaps criteria should be developed to grade particular effects. In particular he suggested that the question of reversible or irreversible effects be addressed and also that public perception of effects should be taken into account. Dr. Schneiderman indicated a similar concern with the question of irreversibility.

With regard to question 3, several individuals indicated that multiplication of what were implicitly log functions to derive the CS was probably inappropriate and that perhaps an additive scheme would be better. They also noted that this would probably greatly change the outcome of the ranking procedures presented by Dr. Durkin.

Two participants made additional comments in their postmeeting memoranda. Dr. Silbergeld stated that the ranking of effects presented in Table 4-2 was biased toward pathological findings (i.e., hyperplasia and necrosis) and that some statements were so unqualified as to be uninterpretable (i.e., "any decrease in reproductive capacity"). She also cited the lack of distinction between "death" and "pronounced life-shortening," the lack of a rationale for why teratogenicity without signs of maternal toxicity was considered more serious than with signs of maternal toxicity, and the absence of consideration of reversibility/irreversibility. Dr. Manson made similar points and stated that a distinction should be made between decreases in reproductive capacity that occur with general systemic toxicity and decreases occurring in the absence of other types of toxicity. Dr. Schneiderman also noted the lack of consideration of reversibility, germ plasm effects, and effects occurring over a lifetime (i.e., reduction in functional ability and reduced IQ), and stated that the use of logarithmic scales for effect and dose required substantially more justification. He concluded that the process is "far from ready to be used for extrapolation to NOELs."

4.3.3. Workshop Statement. A workshop statement was written by Dr. Albert. In addition to summarizing the presentation, the statement included the following conclusion.

"The primary objective of the panel was to critique the approach to rating the toxic effects. Three conclusions were reached by the panel:

- "1. There was general endorsement of the principles used in the approach to developing the composite score.

"2. There were reservations about the scheme presented for ranking the toxic effects; for example, tentative suggestions were made that the minimal effects be lumped into a single category and other suggestions concerned different approaches to giving weights to the various kinds of effects than were done by Dr. Durkin. Other possibilities included assigning weighting factors to the quality of evidence used in defining the composite score.

"3. There was concurrence on the fact that the subject is highly complex and one or two days would be required to evaluate all four aspects of defining a composite score and assigning these scores to reportable quantities of spilled toxic substances. The possibility of turning this problem over to the National Academy was discussed with mixed response."

4.4. USE OF EXPOSURE DATA IN ASSESSING HEALTH RISK

4.4.1. Presentation (R. Bruins, G. Kew). A site-specific health risk assessment is accomplished in three phases including a toxicity assessment and an exposure assessment, which may be conducted concurrently, and an integration step to combine these two (see Figure 4-1). The goal or output of a health risk assessment is to report the numbers of people who are at risk of experiencing adverse effects as a result of a given circumstance (such as uncontrolled waste site or untreated industrial effluent). For noncarcinogens, the output would be the number of people subject to exposures above an ADI, a LOAEL, a FEL, etc., and the duration or frequency of exposure. For carcinogens the result can be expressed as numbers exposed to a given risk level, or as a predicted number of cancer cases. The risk assessment should also be capable of estimating environmental levels or exposure concentrations that can serve as goals for remedial measures.

The risk assessment methodology being developed by ECAO focuses primarily on the toxicity assessment phase (ADI and risk level calculations for single chemicals) and also on methods used in the integration phase (assessment of chemical mixtures, multiple exposure of routes, and response of sensitive subgroups). The goal of this workshop was to discuss the information an exposure assessment can provide and how it should be used. The intent was not to recommend how an exposure assessment should be performed. Some of the questions with which we were concerned include the following: How will the availability or quality of key exposure information affect the assessment procedure? What is the most appropriate endpoint (i.e., exposure concentration or absorbed dose) of an exposure assessment? What special problems arise when more than one chemical is involved?

4.4.1.1. DATA AVAILABILITY AND QUALITY -- An exposure assessment examines the identity of chemicals of concern, their movements and concentrations in various environmental media, and the demographics of potentially affected populations. The types of information useful in conducting a risk assessment are chemical exposure levels, numbers and kinds of people exposed at each level, and exposure durations.

The exposure level is likely to be a critically important factor, but is very difficult to precisely ascertain. It is therefore important to consider the effect of exposure uncertainty upon the overall outcome of the risk assessment. Site assessments could conceivably be requested where the exposure level is unknown. Consider, for example, a situation in which the identity of chemicals at a site is known and release is verified, but lack of time, funds, or data has precluded an exposure assessment. Or consider a

situation where release seems imminent but has not yet occurred. We may readily conclude that without the needed data, no risk assessment is possible. But consider a similar situation, in which an exposure assessment has been conducted, but limited information has required that a large number of assumptions be made to the extent that the uncertainty around the exposure level is extremely large, i.e., several orders of magnitude. This exposure estimate could in effect be as useless as no assessment at all.

Thus, in terms of associated variability, the data may fall anywhere on a continuum from very poor to highly accurate (i.e., where extensive target monitoring has been conducted). Questions to be considered include the following: What level of precision can be expected from a typical exposure assessment? Should our methodology provide guidance as to what is acceptable? How should exposure uncertainty be treated when exposure estimates are integrated with toxicity estimates?

Other types of data may also be unavailable or of variable quality. If exposure levels are given but no information is provided on the size or composition of the exposed population, it may still be possible to complete a health risk assessment. However, the result could be expressed only in terms of effects and would be lacking in the population dimension. This would allow a qualitative judgment as to whether or not a hazard existed, but would not permit an estimate of the associated societal cost. The lack of information about the characteristics of people exposed raises an issue of whether the population should be assumed to be "average" or "sensitive" with respect to physiological, behavioral, or genetic traits that may affect response. Thus, this topic is related to the topic of the "sensitive subgroups" workshop.

As to exposure duration, the assumption of lifetime exposure may be sufficient to indicate whether the situation is acceptable in perpetuity or whether remedial measures need to be taken. However, more specific information on exposure duration, i.e., duration of past exposure and likely duration before remedial measures are completed, could be needed in decisions to relocate people, change water source, etc. What are the impacts if this information is unavailable, and is this an issue that our guidelines need to address?

4.4.1.2. ENDPOINT OF EXPOSURE ASSESSMENT -- The endpoint of an exposure assessment may vary according to the purpose, the substance, or the type of monitoring done. If the substance has been monitored in air, food, soil, or water, exposure may be expressed as the concentration or amount reaching human exchange membranes. If absorption factors are known or estimated, exposure may be expressed as a whole-body absorbed dose. If human tissues or excreta are monitored, knowledge of pharmacokinetics is needed for back-calculating to either a body dose or an environmental concentration. Where multiple routes of exposure may contribute to systemic effects, whole-body dose may be the best indicator of effects. On the other hand, where effects may be route-specific, exchange-membrane concentrations or amounts could be most useful. Therefore, it is important to consider the significance of the exposure endpoint in determining health risk, and to evaluate whether our guidelines should address this issue.

4.4.1.3. **MULTIPLE CHEMICAL EXPOSURE** -- The preceding questions apply to single-toxicant exposures. What additional questions are faced by health risk assessors in interpreting the results of multichemical exposure assessments? For example, consider a site vicinity where exposure to each of two chemicals varies over a wide range. If both were transported by the same route(s), then their respective exposure levels should be directly correlated, and some individuals might be exposed to the highest observed levels of both. Alternatively, if routes differ, the highest exposures may occur to different individuals; this would affect the outcome of the health risk assessment. Thus, it would not be sufficient for an exposure assessment to simply provide ranges of chemical levels over a given area, but correlations among chemicals or routes may also be needed. Guidance on this and other points is needed.

Many other questions are likely to arise in any attempt to conduct a risk assessment using this methodology. Hence there is a need to conduct trial assessments in order to detect remaining problems. Another goal of this session is to identify available exposure assessment data that would be suited to this purpose. Assessments including data on more than one chemical and on the exposed population would be most useful. Participants are requested to provide suggestions and/or exposure data of which they are aware.

4.4.2. **Discussion.** Dr. Wyzga of the Electric Power Research Institute (EPRI) briefly discussed EPRI's current approach to assessing exposure to atmospheric emissions. From information on transport and transformation, an estimate of the atmospheric concentration of a given pollutant is made.

These data are combined with a demographic model of the exposed population that includes health status and activity levels as covariants. Similar approaches are used for estimating the contribution of the other media (i.e., water and food) to the total exposure; that is, whatever data are available are used in models of the movement of pollutants within and between the media to determine exposure.

Dr. Nisbet stated that in his experience the modeling approach was of no use in gauging exposures resulting from hazardous waste sites because exposure conditions are site-specific and therefore do not fit the models. The monitoring data tend to show wide variability in space and time and that, although a log-normal distribution is desired, such a distribution is rare. Dr. Silbergeld pointed out that an important factor missing in exposure assessments is the environment-human interface, i.e., how people's behavior influences their exposure to toxic substances. She also expressed the concern that, because little information is available on the background rate of various diseases in the population, the health status of a potentially exposed population is not considered in exposure assessments. Other participants also commented that both behavioral and health status data are needed (Andelmann, Mehlman, Hattis).

4.4.3. Workshop Statement. Dr. Mehlman, chairman of the workshop, submitted the following summary statement:

"We assume that the type and amount of waste will be reasonably well characterized (but may be deficient in some cases).

"Exposure assessments are resource limited and data-limited, and exposures are variable in space and time; therefore, exposure cannot be characterized by a single number.

"The following data are desirable for characterizing exposure: monitoring data from air, water (surface and ground), foodstuffs (especially fish), and soil must be determined to adequately establish the level of substances present. Tissue/excreta monitoring in humans or animals from the area is extremely valuable in assessing exposure.

"Human behavioral observations in the area should be made to identify exposure routes or sensitive individuals.

"Attention should be given to proper locations of monitoring wells.

"The output should be explicit as to the variability associated with exposure, both in space and time.

"Monitoring data and exposure assessments come from a wide variety of sources within and without U.S. EPA. Close communication between those responsible for each phase must be encouraged, especially if a second phase of monitoring can be done.

"We recommend that the Agency commission a paper discussing the integration of environmental monitoring data, exposure data, and health data, including the role of epidemiology of exposure."

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